THE NATURE OF ESSENTIAL HYPERTENSION

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RECENT correspondence in this journal has shown that opinion is divided between two views of the nature of essential hypertension.

The older view, to which it seems that most subscribe, is that essential hypertension is a specific disease entity, and that subjects with and without the disease can be separated sharply on the basis of their arterial pressures. This hypothesis conforms to the general belief that disease represents a qualitative deviation from the norm, and it has led to investigations on inheritance assuming that the disease is the manifestation of a single gene believed to behave as a mendelian dominant.

The new view, for which we and our colleagues are largely responsible, is that essential hypertension represents a quantitative and not a qualitative deviation from the norm; that there is no natural dividing line between normal and abnormal pressures; and that any attempt to divide pressures sharply into normal and abnormal is artificial. Should it prove that the genetic element in hypertension—indeed in the determination of arterial pressure generally—is multifactorial, this hypothesis would receive strong support. Blood-pressure would then be inherited as a graded character like height, and the mode and degree of inheritance would be the same whether the pressure is below the norm or so far above it as to constitute essential hypertension. This hypothesis is in full accord with the quantitative relationship between arterial pressure and its adverse effects on expectation of life and on the cardiovascular system (see Pickering 1955).

Controversy centres around the nature of the inheritance. It was reopened by Platt's (1959a) article in which he showed clearly that the frequency distribution curves for sibs, aged 45–59, of propositi, aged 45–59, with essential hypertension, had dips at 150 systolic and 90 diastolic "which is exactly the figure most commonly chosen by clinicians as the dividing line between normal and high blood pressure in middle aged subjects". Platt took his data from the work of Sobye (1948) and of Hamilton et al. (1954c). He concluded:

"The final proof as to whether essential hypertension exists as an entity will have to wait until a prospective survey lasting at least twenty years has been made over a large unselected population to see whether with advancing years they segregate into two groups, those whose pressures steeply rise and those whose pressures remain little affected. Until this is done I shall remain unconvinced that the work of Pickering and his colleagues has disposed of the concept of the entity of essential hypertension."

Platt's paper was followed by one of Morrison and Morris (1959) which favoured the view that hypertension without apparent cause is inherited as a dominant and is a specific disease. *The Lancet* (1959) commented: "We find this new evidence that essential hypertension is a specific disease both convincing and more in keeping with its clinical behaviour".

Here we re-examine the two hypotheses and the controversial genetic evidence.

The Evidence Re-examined

We begin by considering the evidence for the hypothesis that essential hypertension is the expression of a single gene behaving as a mendelian dominant. This hypothesis has been stated by Platt as follows:

"This concept of essential hypertension as an inherited tendency to develop high blood-pressure in middle life presumes that there are two populations, one in which blood-pressure rises significantly in middle age, often reaching heights at which it seriously contributes to mortality, and another population in which blood-pressure rises only very little if at all with increasing years."

The evidence put forward for this hypothesis is the occurrence of the disease in three generations, equality of numbers of affected and unaffected sibs, and bimodality of frequency-distribution curves in sibs; we may also consider the rate of rise of pressure with age and the problem of gene frequency.

THE DISEASE IN THREE GENERATIONS

Weitz (1923) and Platt (1947) have both been impressed by this evidence for mendelian dominant behaviour. The evidence is either the occurrence of hypertension, or death from stroke or sudden heart-failure, in three successive generations. If we accept, as they do, a pressure of 160 or over as proof of hypertension, then we may calculate the probability of such an occurrence in an unselected group of families without making any assumptions about inheritance. The frequency of pressures of 160 and over in Hamilton's (1954a) population sample aged 55–59 was 23% in men and 38% in women. Assuming both parents and all four grandparents of a given individual achieve this age, the chances of the pressure exceeding this value in one of his parents and one of his corresponding grandparents, is then 37%. We attach no importance to this precise figure, since it depends critically on the arbitrary figures chosen to represent hypertension, on the circumstances in which blood-pressure was measured, and on the age-group considered. However, it is evidently possible, by making up families at random, to obtain a greater frequency of hypertension in the two generations preceding the propositus than indeed was reported as evidence for inheritance by Weitz and Platt. For Weitz (1923) observed 6 families out of 82 considered, and Platt (1947) 4 out of 54—a proportion that is scarcely strong evidence for dominant inheritance.

RATIO OF AFFECTED AND UNAFFECTED OLDER SIBS

This was studied by Weitz (1923), who found 1:1 ratio between them when 160 systolic was taken as the dividing line, and sibs who had died from heart-disease and stroke were added. The ratio is clearly determined by the choice of a dividing line and the age-group to which it is applied. In Hamilton et al.'s (1954a) population sample, a 1:1 ratio can be got by choosing a similar dividing line and choosing women in the seventh decade.

ARE THE DISTRIBUTION CURVES OF BLOOD-PRESSURES IN FIRST-DEGREE RELATIVES BIMODAL?

Platt (1959a) plotted the frequency distribution of sibs aged 45–59 years of propositi aged 45–59 years with hypertension. Those derived from Sobye's (1948) data had a conspicuous dip at 140 and 150 systolic and at 90 diastolic: those derived from Hamilton et al.'s (1954c) data had dips at 150 systolic and 90 diastolic. We have found that these dips are not due to combination of the sexes, since they persist in the same places when the sexes are separated, even though the distribution curve for females is, as a whole, shifted to the right. Besides bimodality, chance or digit preference might be responsible for these dips. Apart from two superimposed separate populations, there are other causes for bimodality. We have therefore examined the frequency-distribution curves for each sex and in all decades in both Sobye's and our hypertensive relatives and in our control relatives with these possibilities in mind.

Relatives of Hypertensive Propositi

The first-degree relatives of all Hamilton's and Sobye's hypertensive propositi have been divided into males and females, and frequency distribution curves have been plotted for age-groups 10 to 29, 30 to 39, and each succeeding decade to the eighth. For systolic pressures a dip at 150 was found in 9 out of 12 curves in Sobye's series and in 3 out of the 12 curves for Hamilton's series. For diastolic pressures the corresponding frequencies of a dip at 90 are 8 out of 10 times in Sobye's series, 2 out of 10 times in Hamilton's series; the distribution curves for diastolic pressure in age group 10–29 were so narrow, and Sobye's series had so few points, that they have been omitted. As an approximate index of the size of the dip, the number of subjects having pressures of 150+155 mm. Hg was expressed as a fraction of the mean for the numbers respectively at 140+145 and 150+155. The same has been done for numbers with diastolics of 90+95 as fractions of those 80+85 and of 100+105 respectively. The results are for Sobye's series:

Systolic:
All relatives, 0·49.
Relatives aged 45 to 59, 0·45.
Diastolic:
All relatives, 0·55.
Relatives aged 45 to 59, 0·61.

and for Hamilton's series:

Systolic:
All relatives, 1·02.
Relatives aged 45 to 59, 0·90.
Diastolic:
All relatives, 0·94.
Relatives aged 45 to 59, 0·73.

Thus the dips are much more conspicuous in Sobye's series.

Fig. 1 compares the frequency-distribution curves of diastolic pressure in females in the successive age-groups of the two series. The curves not only show the more constant dip in Sobye's series; they also show how constant in position it remains. The same is true for the systolic curves. As decade succeeds decade, the distribution curves move to the right and spread out—but the dips at 150 and at 90 tend to stay. If these depressions represent bimodality, it is a very curious one; for the bulk of subjects seem to transfer themselves from one side of the dip to the other as age advances. This bimodality cannot represent two populations in one of which blood-pressure rises little with age and in the other steeply. In fact, if the dip is real it can mean only one thing—that the transition from pressures of 140 and below to those of 160 and above is achieved much more quickly at all ages than other transition of comparable size.

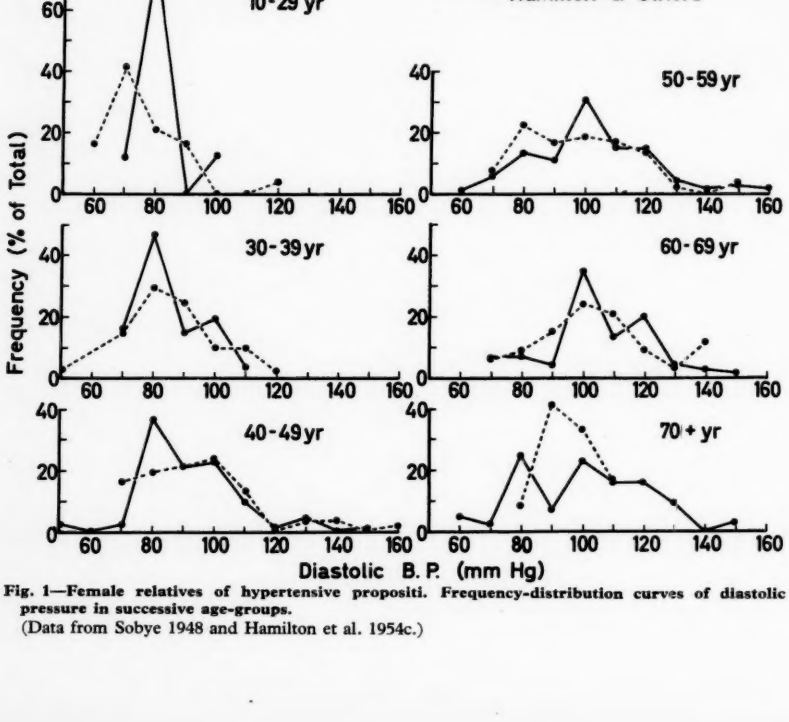

Fig. 1—Female relatives of hypertensive propositi. Frequency-distribution curves of diastolic pressure in successive age-groups.
(Data from Sobye 1948 and Hamilton et al. 1954c.)

Tables I and II from Miall's follow-up in the Rhondda Fach show the frequency distributions of change of systolic pressure over four years in females and males arranged according to the mean of the pressures recorded in the first and second survey. Each distribution is remarkably regular and shows no sign of being separated into two parts; in females the mean change at 150 mm. Hg is indeed slightly larger than in the adjacent groups, but to a small degree. In males, 150 marks the beginning of an increase that continues steadily to 190 mm. Hg.

However, the real importance of these tables is their relevance to the single-gene hypothesis. On this hypothesis even in four years there should be a clear segregation into those whose "pressures rise significantly" and those "whose pressures rise only very little if at all". No such segregation is seen.

The constancy of these dips at 150 and 90 and their presence in both sexes makes it unlikely that they are due to chance.

TABLE I—DISTRIBUTION OF CHANGES OF PRESSURE IN FOUR YEARS BY AVERAGE OF PRESSURES AT BEGINNING AND END OF PERIOD. FEMALES, SYSTOLIC

Change of pressure in 4 years (mm. Hg)	Mean of starting and final pressures (mm. Hg)																	Total
	80–	90–	100–	110–	120–	130–	140–	150–	160–	170–	180–	190–	200–	210–	220–	230–	240–	250–	
70–80	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1
60–	..	..	..	..	..	..	..	..	..	..	2	1	1	1	..	..	..	..	5
50–	..	..	..	..	..	..	..	..	..	..	2	..	..	..	..	..	..	..	2
40–	..	..	..	..	..	1	2	1	1	1	..	..	1	1	1	1	1	1	12
30–	..	..	2	9	4	6	3	3	1	2	4	1	1	..	..	..	..	..	36
20–	..	5	5	16	11	14	4	6	5	5	5	1	..	1	..	..	..	..	78
10–	..	4	16	34	26	18	10	6	3	3	2	2	2	1	..	..	..	..	127
0–	..	3	23	41	37	21	13	8	8	1	2	1	..	..	..	..	1	..	159
−10	..	3	12	26	29	18	8	4	2	2	..	2	..	..	1	..	..	..	107
−20–	..	..	3	8	8	6	4	1	2	1	..	..	1	..	..	1	..	..	35
−30–	..	1	..	3	4	3	2	..	..	2	..	1	..	..	..	..	..	..	16
−40–	..	1	..	..	..	..	1	1	1	1	..	..	..	..	1	..	1	..	7
−50–	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	1
−60–	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
−70–	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
−80–	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	1
Total	..	17	61	137	119	87	47	30	23	18	17	10	7	5	3	2	3	1	587
Mean change	..	4·85	4·80	5·57	2·75	5·83	4·41	9·50	6·85	7·50	29·56	17·50	9·64	18·5	−0·83	12·50	2·50	42·50	..

Conscious or unconscious discrimination against particular figures is clearly a possible explanation. The frequency of such a practice is exemplified by the following instructions from an insurance company to their examining doctors: " If the Systolic Pressure is 140 mm. Hg or more, or the Diastolic Pressure is 90 mm. Hg or more, please take further readings ". This is not an unimportant consideration, since about a third of Sobye's and half of Hamilton's measurements were made by either family or hospital doctors.

Both Sobye and Hamilton et al. began their observations with the assumption that subjects could be divided into those with and without hypertension. They thus had predominantly in mind the question " has the relative got hypertension or not? " and thus the unconscious incentive to assign borderline cases to one side of the line or the other. Sobye worked out all his results in terms of this hypothesis; moreover, since Sobye made repeated measurements he had a greater opportunity to discriminate against borderline values than Hamilton and his colleagues, who took only one measurement. Sobye states that " the values were not recorded at greater intervals than 5 mm. Hg ". " Measurements were undertaken at intervals of 5 minutes until basal and stable values were obtained which generally took ab. 5 to ab. 45 minutes. The cuff was left on the arm but relaxed between measurements and the soothing and diverting conversation was continued ". Despite the numerous readings taken, and his opportunity for fine measurement, 73% of the values he finally adopted of systolic and 74% of those for diastolic pressure end in 0. His, then, was rather a coarse assessment of arterial pressure, and the opportunity for digit preference to affect the numbers assigned to neighbouring 10s correspondingly great.

Hamilton and his colleagues took their pressures to the nearest 5 mm. Hg and took one reading. They did not try to measure more closely than 5 mm. because they doubted the significance of more accurate readings in view of the diurnal variability. When, however, a single reading is taken, pressure in the cuff is raised to 200 mm. Hg or over and allowed to fall until sounds first appear and then suddenly diminish—incidents which the observer correlates with the position of the mercury meniscus relative to the adjacent scale. Here again there is scope for digit preference between adjacent 10 mm.

The difference between the sizes of the dips at 150 and 90, and the greater opportunity for digit preference in Sobye's series, are evidence for this explanation.

Relatives of Propositi Without Hypertension

Hamilton et al. (1954c) collected this series as a control for the relatives of hypertensive propositi. We have plotted the frequency-distribution curves for the same age-groups as for the hypertensive series but with the sexes combined. Dips at 150 and 90 were not seen. We have not tried to express the numbers at 150 and 90 as fractions of the means of adjacent groups above and below, because in this series the frequencies are falling at these points and the fractions would be misleading.

The absence of any appreciable dip in the control series is against digit preference being the explanation of the dip in the hypertensive series. However, this argument is not conclusive, because the curves for hypertensive relatives were much flatter at this point and dips were thus more easily displayed, and because in fact the dips were present only in 5 out of 22 of the corresponding frequency-distribution curves of systolic and diastolic pressure by decades in the hypertensive relatives.

Our conclusion from a critical examination of this evidence is that the dips to which Platt has rightly drawn attention might represent bimodality, but they might also be due to discrimination against certain figures, or digit preference. If they do represent bimodality it is not between two populations having the characteristic rates of rise of pressure with age postulated by Platt. Because

TABLE II—DISTRIBUTION OF CHANGES OF PRESSURE IN FOUR YEARS BY AVERAGE OF PRESSURES AT BEGINNING AND END OF PERIOD. MALES, SYSTOLIC

Change of pressure in 4 years (mm. Hg)	Mean of starting and final pressures (mm. Hg)																Total
	80–	90–	100–	110–	120–	130–	140–	150–	160–	170–	180–	190–	200–	210–	220–	230–	240–	
70–	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1
60–	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	1
50–	..	..	..	..	..	..	1	..	2	..	1	1	..	..	..	..	1	6
40–	..	..	2	1	4	..	1	..	..	1	2	2	..	..	1	..	..	14
30–	..	..	..	3	3	8	4	4	4	1	1	..	..	..	..	..	..	28
20–	..	2	8	10	16	16	9	6	1	2	1	..	..	..	..	..	..	71
10–	1	2	17	52	51	24	11	3	3	..	..	2	..	..	..	..	..	126
0–	..	4	7	25	44	20	15	7	1	2	3	..	..	..	..	..	..	128
10–	..	..	12	11	28	21	15	4	3	2	..	..	1	..	..	..	..	97
20–	..	..	3	4	13	8	7	..	2	1	..	..	..	..	..	..	..	38
30–	..	..	..	1	1	1	..	..	1	..	..	..	..	..	..	..	..	4
40–	..	..	..	..	1	..	..	1	..	..	..	..	..	..	..	1	..	3
50–	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Total	1	8	49	87	141	98	63	25	17	10	9	5	1	..	1	1	1	517
Mean change	12·5	9·75	7·19	7·54	4·11	6·58	5·83	10·10	12·50	16·50	29·16	32·50	−7·50	..	42·50	−37·50	52·50	

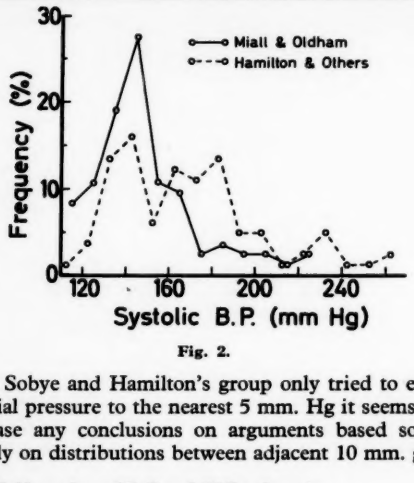

Fig. 2.

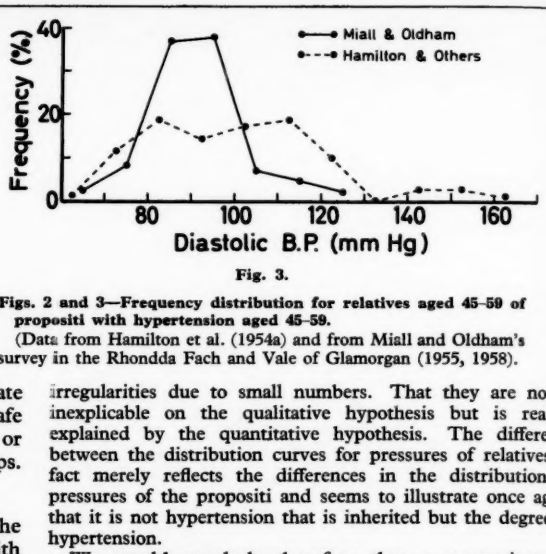

Fig. 3.

Figs. 2 and 3—Frequency distribution for relatives aged 45–59 of propositi with hypertension aged 45–59.
(Data from Hamilton et al. (1954a) and from Miall and Oldham's survey in the Rhondda Fach and Vale of Glamorgan (1955, 1958).

both Sobye and Hamilton's group only tried to estimate arterial pressure to the nearest 5 mm. Hg it seems unsafe to base any conclusions on arguments based solely or chiefly on distributions between adjacent 10 mm. groups.

The Evidence from Miall and Oldham's series

Miall and Oldham (1955, 1958) set out to explore the possibilities raised by Hamilton and his colleagues with two major improvements in technique: their propositi were truly a random sample and a single observer (Miall) measured the arterial pressures to the nearest 5 mm. Hg below.

Figs. 2 and 3 show the frequency-distribution curves for 84 sibs aged 45–59 derived from propositi aged 45–59 with diastolic pressures of 100 mm. Hg or above, and the corresponding curves for Hamilton's series. Miall and Oldham's readings show no preference for 0s, since, of the 83 systolic readings of 220 or below, 42 ended in 0, while of the 82 below 120 diastolic, 45 ended in 0. The curve for systolic pressure shows a slight flattening at 150, but does not seem bimodal; that for diastolic pressure shows no evidence of bimodality.

Both systolic and diastolic curves for Hamilton's data show the dip to which Platt drew attention. Quite apart from this they differ conspicuously from those of Miall and Oldham's data in being much flatter, owing to a less pronounced peak, and a considerable excess of values over 160 mm. Hg. systolic and 100 diastolic. These differences clearly reflect differences in the frequency distributions of pressures of the two sets of propositi shown in figs. 4 and 5. Miall and Oldham's propositi represent a " cut off " from a population sample, and, as might be expected, the frequency is maximal with the lowest pressures and sharply declines. Hamilton's propositi, however, were drawn from patients presenting with symptoms. They naturally show a pronounced deficiency at the lower and an excess at the higher pressures.

The qualitative hypothesis provides no explanation for the differences between Miall and Oldham's first-degree relatives of hypertensive propositi on the one hand and Hamilton's on the other. If propositi aged 45–59 with diastolic pressures of 100 and more have essential hypertension, as those who support the single-gene hypothesis aver, then the frequency-distribution curves for the Miall and Oldham and Hamilton relatives should be alike, allowing of course for irregularities due to small numbers. That they are not is inexplicable on the qualitative hypothesis but is readily explained by the quantitative hypothesis. The difference between the distribution curves for pressures of relatives in fact merely reflects the differences in the distribution of pressures of the propositi and seems to illustrate once again that it is not hypertension that is inherited but the degree of hypertension.

We would conclude therefore that a comparison of Miall and Oldham's and Hamilton's data reveals features that are inexplicable by the qualitative but are in full accord with the quantitative hypothesis.

RATE OF RISE OF PRESSURE WITH AGE

It is an essential part of Platt's hypothesis that what is inherited as an expression of the dominant gene is a tendency for the arterial pressure to rise faster with age than it does in those lacking the gene. Hamilton and his colleagues found that the rates of rise of systolic and diastolic pressure with age did not differ significantly in (1) their population sample, (2) the first-degree relatives of propositi without hypertension, and (3) the first-degree relatives of propositi with essential hypertension, except for a faster rise of systolic pressure with age in the male hypertensive relatives.

Table III summarises the rates of rise of pressure with age in relatives of propositi aged 45–59 with and without hypertension. The sexes are combined since there was no material difference between them. It will be seen that if relatives of all ages are considered, the rate of rise differs significantly between the two sets of relatives in Hamilton's series but not in that of Miall and Oldham. When relatives aged 35 and over are considered separately, a similar trend is found, the difference being significant for systolic and nearly significant for diastolic in

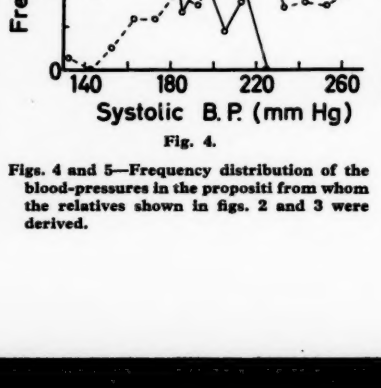

Fig. 4.

Figs. 4 and 5—Frequency distribution of the blood-pressures in the propositi from whom the relatives shown in figs. 2 and 3 were derived.

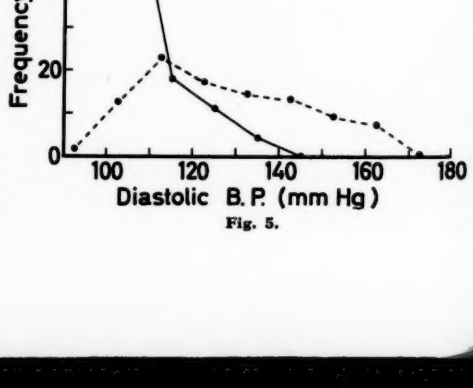

Fig. 5.

Hamilton's series but less pronounced in Miall and Oldham's series.

Two points require comment. First, in Hamilton's series the disparity between relatives of normal and hypertensive propositi is increased to the point of revealing a significant difference by restricting propositi to age-group 45–59. Second, a difference between the two sets of relatives is revealed in Hamilton's series but not in that of Miall and Oldham.

Now this is exactly what would have been expected on the quantitative hypothesis and on the known behaviour of blood-pressure with age. A given deviation from the norm at age 30 is represented by a much larger one at age 60. Thus if relatives resemble propositi, the higher the pressures of the propositi the steeper should be the slopes of the rates of rise of pressure with age in their first-degree relatives. The difference in the way propositi were chosen would account for the difference in rates of rise with age being greater in Hamilton's than in Miall and Oldham's series. Restricting the age-group of propositi would account for the differences between the present and previously published comparisons of Hamilton's series. Thus Hamilton and his colleagues were disturbed by the absence of any significant difference in the rates of rise of pressure with age in three of the four comparisons between normal and hypertensive relatives. They wrote (1954c):

TABLE III—RATE OF RISE OF BLOOD-PRESSURE (MM. HG) PER YEAR OF AGE IN FIRST-DEGREE RELATIVES OF PROPOSITI AGED 45–59

—	Propositi without hypertension	Propositi with hypertension	Difference
Relatives of all ages:			
Systolic			
Hamilton et al. ..	0·855 ± 0·129	1·276 ± 0·149	0·421 ± 0·213
Miall and Oldham ..	0·997 ± 0·057	0·968 ± 0·160	−0·029 ± 0·150
Diastolic			
Hamilton et al. ..	0·408 ± 0·080	0·549 ± 0·090	0·141 ± 0·129
Miall and Oldham ..	0·400 ± 0·032	0·261 ± 0·087	−0·139 ± 0·090
Relatives aged 35 and over			
Systolic			
Hamilton et al. ..	0·780 ± 0·189	1·512 ± 0·242	0·732 ± 0·325
Miall and Oldham ..	1·449 ± 0·170	1·766 ± 0·446	0·317 ± 0·446
Diastolic			
Hamilton et al. ..	0·222 ± 0·114	0·413 ± 0·144	0·191 ± 0·194
Miall and Oldham ..	0·219 ± 0·087	0·212 ± 0·248	−0·007 ± 0·235

" Figs. 3 and 4 appeared to show that the pressures of the youngest relatives of hypertensive subjects are divided from the norm to the same extent as their older relatives. The majority of the relatives are sibs and so resemble the propositi in age distribution; this means that on the average the younger relatives are derived from the younger propositi and therefore depart more greatly from the norm. Hence curves which should have shown increasing divergence have become artificially parallel."

While the new comparison may seem to fit Platt's hypothesis, it is thus also compatible with the quantitative hypothesis, from which indeed it could, as the quotation shows, have been predicted.

Now Platt's hypothesis implies that the rate of rise of pressure with age is entirely, or almost entirely, due to the presence, in the populations considered, of people carrying the hypertensive gene. There should thus be a considerable difference between the behaviour of the population at large, in which the rate of rise of those carrying the gene will be diluted by the much larger number of those without it, and the behaviour of the first-degree relatives of affected subjects who share a gene in 50% of cases.

TABLE IV—DISTRIBUTION OF THE MEAN DIASTOLIC PRESSURES OF 119 RELATIVES OF HYPERTENSIVES AND 59 RELATIVES OF NORMOTENSIVES (CRUZ-COKE 1959)

Age (years)	Relatives of normotensives		Relatives of hypertensives	
	No. of cases	Diastolic B.P. (mean and standard error)	No. of cases	Diastolic B.P. (mean and standard error)
10–19	5	65·0 ± 1·75	22	75·1 ± 1·45
20–29	18	71·0 ± 1·65	38	78·9 ± 1·44
30–39	13	75·1 ± 2·40	19	88·8 ± 1·64
40–49	7	76·4 ± 2·09	17	89·0 ± 1·66
50–59	11	81·3 ± 2·65	15	95·3 ± 2·14
60–69	5	80·0 ± 5·10	8	93·6 ± 2·89
	59		119	

The absence of such a difference between the relatives of Miall and Oldham's propositi whose pressures fall below and above the postulated division, and thus between those without and with the postulated specific gene, seems to be conclusive evidence against the qualitative hypothesis, at least in its present form.

Platt (1959b) has cited two papers showing that arterial pressure does not rise with age in certain groups.

Thomson (1950) studied the records of 3343 employees of the Metropolitan Life Insurance Company, whose arterial pressures had been recorded annually from age 40 to retirement at 60 in women and 65 in men. He divided them into three groups according to whether their arterial pressures at any time exceeded 140 systolic and 90 diastolic. Those who never exceeded these values were " normal ", those who frequently exceeded them were " frequently elevated ", and those who always exceeded them were " constantly elevated "; they constituted respectively 74·2%, 14·4%, and 11·4% of the whole. That individuals behave differently in response to age is not disputed and was indeed the conclusion of Hamilton and his colleagues on less direct evidence. Thomson, however, presents no evidence that these differences are inherited. What surprised Thomson was that 66 of the 130 deaths (51%) in the normal group were due to cardiovascular causes, a finding not irrelevant to Morrison and Morris's thesis.

Cruz-Coke (1959) measured the diastolic pressures in (*a*) 119 first-degree relatives of 35 hypertensive patients and (*b*) 59 first-degree relatives of 18 normotensive patients. His numbers were rather small, but the results as summarised in table IV are remarkably similar to those we have found: the arterial pressures are higher at all ages in the relatives of hypertensive propositi and the rates of rise of pressure are similar in the two sets of relatives. He also tabulated (table V) the mean pressures found twelve years before in 170 patients who afterwards became hypertensive (diastolic 105 mm. Hg or above) and 104 patients whose blood-pressure had always been normal (diastolic below 105 mm. Hg). The two series show corresponding differences and again show similar rates of rise with age.

Taken as a whole, these observations strongly suggest that what is inherited is not a tendency for the arterial pressure to rise more steeply with age, but a tendency

TABLE V—DIASTOLIC PRESSURES WHEN FIRST EXAMINED AT MEAN OF 12 YEARS PREVIOUSLY IN 170 SUBJECTS WHOSE PRESSURES REMAINED BELOW 105 DIASTOLIC AND IN 104 WHOSE PRESSURES SUBSEQUENTLY ROSE ABOVE 105 DIASTOLIC (CRUZ-COKE 1959)

Age (years)	Established normotensives		Previously normotensives (at present hypertensives)	
	No. of cases	Diastolic B.P. (mean and standard error)	No. of cases	Diastolic B.P. (mean and standard error)
30–34	62	72·9 ± 0·95	18	84·0 ± 2·93
35–39	45	75·4 ± 1·25	28	87·7 ± 1·68
40–44	30	77·5 ± 1·62	18	88·5 ± 2·65
45–49	18	76·6 ± 1·61	18	90·4 ± 2·62
50–54	8	84·4 ± 4·23	13	95·0 ± 4·05
55–59	7	85·0 ± 2·30	9	95·0 ± 3·05
	170		104	

to higher pressures at all ages. Such is in accord with our own casual or (as it is sometimes called) "clinical" experience, and with that of others. The rate of rise and the pattern of rise is a highly individual experience and in individuals is largely independent of the first recorded pressure.

Holmgren (1955) illustrated this by 19 examples of blood-pressure fluctuations over twenty to thirty-five years from age 31 upwards. Bechgaard (1946) analysed the changes in arterial pressure of 192 men and 553 women with essential hypertension (blood-pressure 160/100 or 180 systolic upwards) over four to five years. Comparing the first and last recorded pressures, 41% showed no change (within 20 mm.), 22% a rise, and 37% a fall. Between 140 and 200 mm. systolic those with the lower pressures tended to show a rise and those with the higher pressures a fall at the second examination. Above 200 mm. there tended to be a rise at the second examination.

TABLE VI—POPULATION SAMPLE (HAMILTON ET AL.). SYSTOLIC PRESSURES OF SUBJECTS AGED 45–49

Age	Systolic pressures (mm. Hg)			
	Less than 160	160 and above	Total	% 160 and above
Females:				
45–49	103	11	114	9·6
50–54	92	39	131	29·8
55–59	67	41	108	38·0
Total	262	91	353	25·8
Males:				
45–49	73	6	79	7·6
50–54	80	7	87	8·0
55–59	46	14	60	23·3
Total	199	27	226	11·9

CALCULATIONS BASED ON SUPPOSED GENE FREQUENCY

Both Sobye and Platt have calculated the frequency of the disease in the population and in the first-degree relatives of subjects with essential hypertension, on the assumption that a single dominant gene is concerned. Platt's calculations were based on a disease frequency of 19–30%; Sobye concluded that "the disease occurs in the population at a frequency of about 30 to 40 per cent.". It is reasonable to work in qualitative terms provided one is convinced that there is a qualitative distinction and that the population, at certain ages at least, can be divided into normals and hypertensives.

If we assume that the population can be so divided, the first difficulty we meet is that the frequencies of affected and unaffected persons are different in the two sexes and in successive age-groups. Table VI shows the percentages of those having pressures of 160 mm. Hg and over in males and females of Hamilton's population sample. To select a particular sex or age is purely arbitrary and critically determines any subsequent calculation.

Even if we assume that a division into normal and affected is possible, a further difficulty arises. The ratios between them calculated respectively on dominant-gene and multifactorial inheritance prove to be so alike that the data fail to differentiate between the two hypotheses.

Given a single gene (or locus), and complete hereditary determination, the genetic correlation between first-degree relatives is 0·5, which corresponds to the proportion of genes they have in common. The effect of dominance is to reduce this figure. Assuming a gene frequency of 0·2, corresponding to Sobye's estimate, the reduction is not appreciable. The figures become 0·44 for parent and child and 0·47 for sibs. Assuming multifactorial inheritance the same correlation (or regression) of 0·5 would be found, but only of course if there were complete hereditary determination of blood-pressures. Thus, if it is assumed that blood-pressure is completely determined hereditarily, the proportions of affected and unaffected will be nearly the same on the two hypotheses. If it is not so assumed, the regressions and correlations have to be determined from the data. How this is done will be discussed later. We have previously shown (Hamilton et al. 1954c) that ratios between affected and unaffected like those found by Sobye are compatible with a modest degree of multifactorial genetic resemblance. Here we merely wish to point out that a choice between the two hypotheses cannot be made on calculations of supposed gene frequencies.

TABLE VII—PROPORTIONS OF AFFECTED INDIVIDUALS IN GENERAL POPULATION AND AMONG SIBS OF AFFECTED PROPOSITI GIVEN DIFFERENT GENE FREQUENCIES

Gene frequency	Proportion of affected in population	Proportion affected among sibs of propositi
5	10	54
10	19	58
15	28	62
20	36	66
25	44	70

Platt pointed out that if, as many people hold, hypertension affects 20–30% of the middle-aged population, giving a gene frequency for the dominant gene of 0·16 to 0·1, the observed proportion of hypertensive sibs should be 64–58%, close to what is observed. This, however, is an insensitive test.

In the limit, if the gene is rare, the expected percentage of affected sibs approaches 50. Table VII shows the expected proportions of affected sibs of affected propositi for gene frequencies of 5–25% corresponding to 10–44% of affected individuals in the population. Platt wrote "if we use the systolic pressure of 150 as the dividing line, the proportion of hypertensive siblings is about 0·5". With 252 sibs, the

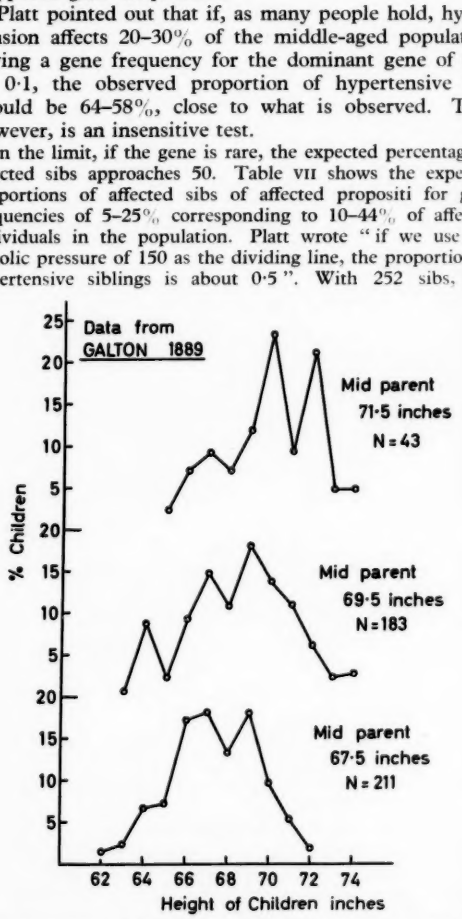

Fig. 6—Frequency distribution of the heights of adult children derived from three groups of parents having mid-parent heights of 67½, 69½, and 71½ inches.

The heights of children are given as 68·2 in. and so on in the table, not as here shown as 68 in. and so on. (Data from Francis Galton's *Natural Inheritance*, 1889, table XI.)

number Platt worked on, the 95% confidence limits are 53 and 65% affected, corresponding to gene frequencies of 4 and 19%; in the population at large the corresponding figures for affected persons are 7 and 34%.

The observed figures of 59% quoted by Platt would fit almost any estimate of the frequency of the disease that has ever been proposed.

MORRISON AND MORRIS'S EVIDENCE

Morrison and Morris (1959) presented "data on the casual blood pressures and length of life of parents of a sample of . . . drivers and conductors of London's buses".

They divided "the parents into those who died in middle age (40–64) and those living to old age (65 and over) on the assumption that this will give a crude subdivision into hypertensive and non-hypertensive groups, or at any rate, into groups with more hypertension and with less." They found that the frequency-distribution curve of blood-pressure of 90 drivers with one or both parents dead in middle age was bifid, while that of 96 drivers whose parents lived to 65 years and more was not. Referring to the first group they describe the curve as "obviously bimodal . . . with a break at about 160 mm. Hg between two groups of almost the same size. Men forming the first peak (at about 140 mm.) may reasonably be regarded as normotensive and those forming the second peak (at about 175 mm.) as hypertensive."

They further found that frequency-distribution curves of ages of death of parent were bifid for 53 fathers of hypertensive (160/95 mm. Hg or over) while not so for 121 fathers of normotensives (under 160/95). They concluded "that in a population sample, an apparently continuous blood-pressure distribution curve may mask a bimodal distribution and that this may be uncovered by means of the inheritance factor, by subdividing the sample according to the ages at death of the parents. This reveals a special group of hypertensive subjects closely associated with premature death in one or both parents."

Two major criticisms may be made of Morrison and Morris's conclusions. First they confuse irregularities of curves with bimodality. If their curves are divided into the two constituent curves alleged to constitute their basic components, the results are to say the least bizarre.

Fig. 6 illustrates this point. It shows three frequency-distribution curves for the heights of children derived from parents whose mid-parent heights were 67·5, 69·5, and 71·5 in., taken from Galton's (1889) table XI from which he derived his concept of filial regression. In preparing this table Galton used a device to adjust female heights to those of males by multiplying them by 1·08 (transmuted female height). These curves show, as indeed do the complete data of table XI, that as parental stature increases, the frequency-distribution curves move to the right, so that the mean height of children is linearly related to that of parents.

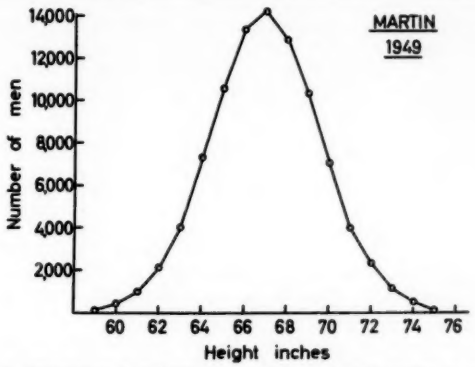

Fig. 7—Frequency distribution of height in 91,163 recruits to the British Army.
(Data from Martin 1949.)

These curves (fig. 6) show dips at 68·2 inches and some might interpret them as evidence of bimodality, exactly as they have interpreted the dips in frequency-distribution curves for arterial pressure. They bear a superficial resemblance to some of the curves in fig. 1, but since none of the other four frequency distributions of table XI show similar dips, they resemble Hamilton's more than Sobye's curves.

No student of the genetics of stature has yet attached significance to these dips. That stature is distributed normally for large numbers is illustrated by the curve for the stature of 91,163 recruits to the British Army measured during the last war (fig. 7).

Second their assumption that a division of deaths at age 65 divides the population into those with and without hypertension is far from the truth.

Table VIII is compiled from the Registrar General's returns for England and Wales for 1935, a year chosen to be representative of a period in which might be expected to die the parents of busdrivers aged 45–60 examined by Morrison and Morris.

TABLE VIII—CAUSES OF DEATH AT DIFFERENT AGE PERIODS, ENGLAND AND WALES 1935

Age-group	Total		Cerebral hæmorrhage so returned and apoplexy lesion unstated cerebral hæmorrhage and apoplexy 82(*a*) 1 & 2		Cerebral embolism and thrombosis 82(*b*)		Diseases of the myocardium 93		Diseases of the coronary arteries 94		Other diseases of the heart 95		Arterio-sclerosis 97		Nephritis 130, 132		Total deaths	Total cardio-vascular (M & F) combined	Proportion of total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F			
40	7181	6675	94	142	25	36	298	253	162	39	52	74	45	41	244	284	13,856	1789	12·91%
45	10,481	8640	229	298	44	73	605	519	375	93	106	112	109	99	360	418	19,121	3440	17·97%
50	14,434	11,571	417	588	108	114	1147	963	733	179	187	174	303	277	649	529	26,005	6368	24·49%
55	19,301	15,219	733	873	199	192	2039	1619	1069	328	280	263	669	488	768	713	34,520	10,233	29·64%
60	24,633	19,867	1082	1227	314	356	3376	2884	1369	534	375	426	1177	928	1072	923	44,500	16,043	36·05%
Total 40–60	76,030	61,972	2555	3128	690	771	7465	6238	3708	1173	1000	1049	2303	1833	3093	2867	138,002	37,873	27·44%
65	28,748	24,685	1436	1667	518	568	4948	4554	1507	764	537	560	1858	1399	1170	1087	53,453	22,575	42·25%
70	30,278	29,511	1683	1948	614	709	6354	6695	1405	839	557	747	2430	2152	1207	1167	59,789	28,507	47·68%
75	26,503	29,658	1371	1874	589	836	6497	7808	924	708	527	713	2376	2387	933	995	56,161	28,538	50·82%
80	26,101	39,952	1011	1962	526	1074	7295	11,913	576	553	434	824	2448	3269	732	909	66,053	33,526	50·76%
Total 65–80	111,630	123,806	5501	7451	2247	3187	25,094	30,970	4412	2864	2055	2844	9112	9207	4042	4158	235,436	113,146	48·06%
Total 40–80	187,660	185,778	8056	10,579	2937	3958	32,559	37,208	8120	4037	3055	3893	11,415	11,040	7135	7025	373,438	151,024	40·42%

The first two columns give the deaths from all causes and the subsequent ones those from causes which might have been associated with hypertension. In those dying between ages 40–64, 27·4% of all deaths were due to diseases commonly associated with hypertension; of those dying from 65 upwards the percentage rises to 48·4. In the population sample of Hamilton and others (1954a) 37% of the males and 74% of the females in the age-group 65–69 had arterial pressures of 160 and over and the percentage rose in each succeeding age-group.

Nor are they justified in concluding that a specific syndrome, essential hypertension, is closely associated with premature death in one or both parents. Only 60% of Sobye's hypertensive propositi had one or both parents dying under the age of 65. In 168 patients now attending the hypertension clinic at the Radcliffe Infirmary 59% of fathers and 77% of the mothers who were dead died aged 65 and over.

CLINICALLY A SPECIFIC DISEASE?

The Lancet (1959) said that the evidence that essential hypertension is a specific disease is more in keeping with its clinical behaviour. Morrison and Morris claim to have identified by epidemiological methods a syndrome "which corresponds to the common clinical notion of 'essential hypertension'; and this supports the hypothesis that essential hypertension is a specific disease entity".

To avoid the common fallacy of circular argument, we may now inquire whether there is any clinical evidence that essential hypertension behaves as a specific disease entity. We know of none, but we know of much to suggest that it does not. Two examples may suffice.

Ayman and Pratt (1931) found that the incidence of early symptoms in their patients with essential hypertension was similar to those found in 50 psychoneurotic subjects with normal blood-pressure.

Fishberg (1954) wrote: "The clinical duration of essential hypertension varies between extremely wide limits. There are instances in which an individual who 'has never been to a doctor' is suddenly seized on the street and expires before the arrival of the ambulance; at necropsy, a coronary occlusion or cerebral hæmorrhage is found, the origin of which in hypertension is revealed by the presence of cardiac hypertrophy and renal arteriosclerosis. On the other hand, the hypertension may last for three or four decades and never do the subject any harm, until he finally dies of some disease having no relation to the hypertension. These pictures constitute the extremes, and the vast majority of instances of essential hypertension fill all conceivable intermediary gaps between them."

Discussion

Having thus examined the evidence that essential hypertension is the manifestation of a single dominant gene, we find it wanting.

The alternative hypothesis—that arterial pressure is inherited polygenically over the whole range, and that the inheritance is of the same kind and degree in the so-called normal range as in that characteristic of essential hypertension—is in general conformity with biological theory and with the facts of observation. Just as stature, the classical human example of polygenic inheritance, is the sum of a number of separate bones and tissues, so is the arterial pressure the resultant of a number of discrete components of the cardiovascular system. One need only mention the radii of different parts of the vascular system, the lengths of the vessels constituting the resistance, their elasticity, the chemical composition of the body fluids, the action of the heart, and the behaviour of the reflex mechanisms regulating arterial pressure. To suppose that all this represents the effects of a specific enzyme formed by a specific gene would indeed be a revolutionary hypothesis and should require exceptionally cogent evidence in its favour.

The evidence reviewed here proves to be more closely in accord with the idea of quantitative resemblance between hypertensive relatives, and thus with polygenic inheritance. Perhaps the most important evidence for this hypothesis comes from the use of an age-and-sex-adjusted score for arterial pressures. And since the use of this score has been criticised (*Lancet* 1959) a few words may be said in its defence.

The method was introduced so that the behaviour of arterial pressure in the population could be studied quantitatively in terms of the quantity measured and not qualitatively in terms of arbitrary divisions into normal and hypertension. The score "for any individual represents the number of mm. Hg., in units of 5 mm., by which the observed pressure, systolic or diastolic, exceeds or falls short of the population average for that age and that sex, the scores being made fully comparable by further adjusting them to the corresponding value as at age 60 years." In a word, the scores are simply mean deviations, with additional allowance for the fact that variance also increases with age.

On either hypothesis, single-gene or multifactorial, allowance for age must be made in some form or other. Assuming a qualitative distinction, the appropriate method is to allow, as Sobye did, for increasing rate of manifestation. On the other hand, assuming quantitative variation the appropriate method is the one we adopted, or some other method which is similar in principle. It was shown that, applied to a population, the scores are in fact independent of sex and very nearly independent of age. The adjusted scores have also at least this empirical justification—that the measures of resemblance of subjects to fathers, mothers, brothers, sisters, sons, and daughters turn out not to differ significantly (Hamilton et al. 1954c).

In their population studies Miall and Oldham (1958) calculated the regression coefficients for age-adjusted scores of individual classes of relatives on their propositi. Significant differences were found in only 3—namely, the regression coefficients of diastolic scores for fathers, mothers and brothers on their female propositi; the rest of the 24 possible relationships were homogeneous. The relatives are of course of very different mean ages and it would be rather surprising if such a correspondence were produced by chance by the use of a method inherently inappropriate to the material investigated.

It is no part of our thesis that the method is perfect, but so far as we know no better has yet been devised. To use some method of allowing for the effects of sex and age is accepted practice in biometrics. Galton (1889) had to "transmute" his female heights to make them comparable with those of males to investigate the inheritance of stature. Stocks (1930) used a device similar in principle in investigating resemblance in twins. Analogous methods are universal in the treatment of intelligence-test scores in children.

Using the age-and-sex-adjusted score and three methods of calculating the resemblance between first-degree relatives of hypertensive propositi Hamilton et al. obtained by each method a regression coefficient of about 0·2. Miall and Oldham, investigating a true random sample of the populations of the Rhondda Fach and Vale of Glamorgan, obtained regression coefficients for relatives on propositi of $0{\cdot}224 \pm 0{\cdot}022$ for systolic and $0{\cdot}178 \pm 0{\cdot}024$ for diastolic scores, and these were independent of the blood-pressures of propositi. The close similarity in the quantitative resemblance between first-

degree relatives, whether their propositi were chosen because they presented as patients with essential hypertension or chosen at random from the population at large, is very strong evidence for the inheritance being quantitative and the same over the whole blood-pressure range. This conclusion receives new support from the observations of Cruz-Coke from Chile, already described. He gives the following mean scores: for hypertensive propositi +53·1, for hypertensive relatives +10·0; for normotensive propositi −15·3, for normotensive relatives −4·0. The crude overall regression coefficient for relatives on propositi is then $\frac{10+4}{53{\cdot}1+15{\cdot}3} = 0{\cdot}20$. The close similarity of this value to those obtained in a different continent and the other hemisphere is striking.

The difficulty with regressions calculated on the basis of continuous variation is that very large numbers are needed before significant deviations from simple linear regressions can be detected. Nevertheless the numbers are now fairly ample; and it does appear, as suggested, that a single regression of a little more than 0·2 accounts for the measures of resemblance to subjects of first-degree relatives of all kinds, and holds for all levels of arterial pressure from the highest to the lowest.

In a critical appraisal of evidence it would be wrong to avoid voicing the doubt whether the resemblance found between blood-pressures of close relations can be accepted as valid evidence for inheritance. Hogben (1957) and others have pointed out that close relatives tend to share not only a common inheritance but also a common environment. Even the greater resemblance between the arterial pressures of identical than of non-identical twins demonstrated by Stocks (1930) and others may only mean that the former tend to live more nearly identical lives than the latter. On this issue we have no conclusive evidence to offer. Certain family resemblances undoubtedly have a genetic basis, and the resemblance in blood-pressure here summarised is most simply explained on a genetic basis.

That environmental factors contribute materially to arterial pressure is suggested by the relatively small coefficient of resemblance—0·2 for blood-pressure as against 0·5 for stature (Pearson and Lee 1903). However, the much greater diurnal variability of blood-pressure than of height contributes appreciably to this disparity. It is tempting to suppose that environmental factors are largely responsible for the rate and pattern of the rise of pressure with age. Miall and Oldham (1958) found that for a given age and sex the arterial pressure was lower the greater the number of children, for those who had undertaken hard physical work and for those who ingested much salt. In his repeated determinations after four years, Miall (1959) observed smaller rises in those with large families and in females who ate much salt, but not in those who did hard physical work. Much thus remains to be done to define and measure environmental influences. We cannot, however, leave this subject without referring to the very close accord between the mean values obtained for corresponding 5-year age-groups of populations so various as the inhabitants of Paddington (London), the mine-workers and agricultural workers of South Wales (Miall and Oldham 1955, 1958), farm workers of the United States (Gover 1948) and the tea workers of Assam, India (Wilson 1958). That genetic and environmental factors so various should have produced such similar mean end results is a phenomenon that challenges explanation.

Finally, as to the nature of so-called essential hypertension. We find the evidence that it represents a specific disease entity, a qualitative deviation from the norm, wanting in every particular. This evidence is compatible, however, with the view that it represents a quantitative deviation to which inheritance makes a modest graded contribution. Environmental factors as yet unspecified and unquantified are probably more important.

The idea that this new quantitative hypothesis will inhibit research is one that we do not understand. The history of new ideas does not suggest that they stop inquiry: they stimulate it. And if this new idea is more closely in accord with the facts than the old, it seems not impossible that the new idea may lead to a better understanding of the nature of the disease. After all, the fruits of the old idea are scarcely impressive.

Summary

Essential hypertension is looked at in two ways. The old idea is that the disease is a specific entity, a qualitative deviation from the norm. The new idea is that it is the consequence of a quantitative deviation from the norm.

Controversy centres on the nature of the inheritance, the old idea drawing support from evidence favouring a single gene, the new idea from evidence favouring multifactorial or polygenic inheritance.

The evidence for single-gene inheritance is unsatisfactory. More probable is multifactorial inheritance as in stature, arterial pressure being inherited as a graded character over the whole range included in the conventional notations "normotension" and essential hypertension.

The new hypothesis should stimulate inquiry. If it is right, the inquiry may even be more rewarding.

We are indebted to Dr. W. E. Miall for the use of his data.

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"... Throughout an un-nursed life I've been sentimental about nurses, seeing them as angels of pity and comfort and always giving them my seat in trains. I think now that I have been right about most of them. But some are diminished by the enjoyment of bossy authority, some throw off a good deal of their kindness with their squeamishness, and some quarrel too openly and pettily in front of the patients, usually about infringements of territory. All of them have sycophantic convulsions when the doctors are around (which the doctors contemplate too placidly): and all of them are slaves to routine, which begins at 5.30 A.M. with a cup of tea."—C. H. ROLPH, *New Statesman*, May 14, 1960, p. 708.

REDUCTION OF INTRACRANIAL PRESSURE WITH HYPERTONIC UREA

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INCREASED intracranial pressure is one of the commonest and most troublesome problems confronting neurological surgeons. It is responsible for many of the symptoms of expanding intracranial lesions, for much difficulty encountered at operations, for complicated convalescence, and for incomplete recovery. The " tight " brain is well known: when the dura is opened the brain bulges, and, unless the pressure can be relieved, it may burst. Short of this, increased pressure limits access to deepseated lesions, and it may be responsible for unnecessary damage to the brain by vigorous retraction.

Among the measures taken to reduce the pressure are elevation of the head (which lowers the venous pressure within the cranium), removal of cerebrospinal fluid (C.S.F.) by ventricular puncture (or less often by lumbar puncture), and " dehydration " by intravenous infusion of hypertonic solutions such as sodium chloride, glucose, or sucrose. More recently anæsthetic techniques have contributed—e.g., by induced hypothermia, the use of ganglioplegic drugs, or " controlled " respiration of the curarised patient. But occasionally, for one reason or another, none of these methods is adequate. This report is concerned with the use of another substance, urea, which seems superior to and more generally effective than any other in reducing intracranial pressure. It was recommended by Javid (1958), whose account should be read by all interested in the subject. Our experience of its use in 129 patients in the United Oxford Hospitals during the past eleven months is in general agreement with his findings.

Javid records that Fremont-Smith and Forbes (1927) observed a remarkable reduction in the C.S.F. pressure of cats after the intraperitoneal injection of hypertonic urea. They stated that " its lack of toxicity and its ready elimination by normal kidneys suggest the possibility of a clinical application ". But this suggestion lay fallow for nearly a quarter of a century until Smythe et al. (1950) found that, on an equiosmolar basis, urea was more effective than glucose in reducing the C.S.F. pressure in monkeys.

In 1954, Javid and Settlage used urea for the first time in man, and two years later (1956) they reported encouraging results in 21 patients. In 1958, Javid described with more confidence the results in 300 patients, taking the view that " urea is a highly useful and safe agent for reducing intracranial and intraocular pressure. It is far superior in every respect to all other agents commonly used for this purpose ". He found that doses of 1·0–1·5 g. per kg. body-weight were effective and well tolerated, and that 10% invert sugar solution was the best agent for dissolving the urea crystals. With 30% urea in 10% invert sugar he observed no hæmolysis, as in experimental animals which had had urea with other solutes.

Method

We have largely followed the method of Javid (1958) and have given most of our patients 1·0–1·5 g. urea per kg. body-weight intravenously as a 30% solution in 10% invert sugar.

The urea solutions we used for these cases were prepared under the direction of Mr. W. Trillwood, chief pharmacist to the United Oxford Hospitals.

The urea was made up as a 60% solution in distilled water, and sterilised by filtration. Because the solution is not stable indefinitely, it was stored in sterile bottles at 2–5°C to reduce the rate of decomposition to a minimum. It should not be kept longer than twenty-one days. Just before use the solution was allowed to come to room temperature and was mixed with an equal volume of sterile 20% invert sugar solution.*

The infusion is given by gravity into a vein in the arm or leg. When a protracted effect is required, we have found that the optimal rate of administration is about 60 drops per minute, as Javid recommended. The effect on the intracranial pressure is seen within fifteen to twenty minutes of starting the infusion, and an adequate reduction in pressure persists for four to eight hours.

But we have also given the infusion much more rapidly without apparent ill effects. When used for craniotomies, where a greater reduction in brain bulk is desired for a shorter time, we have given the total dose within fifteen or twenty minutes. We find it convenient to begin the infusion at the same time as the induction of anæsthesia.

Effects of Urea Infusion

At Operation

Reduction in brain bulk is the most notable effect. When, for instance, a frontal osteoplastic flap is raised, as for the exposure of a pituitary tumour or basal aneurysm, the dura falls away from the bone edges at the margins of the opening, and its whole surface is crinkled. When opened, the brain likewise falls away from the dura, and a space of as much as 2 cm. may be left between the frontal lobe and the posterior surface of the frontal sinus. Even in cases of expanding lesions within the brain, with gross increase in intracranial pressure, the dura is quite slack, and since using urea we have not had to tap the opposite ventricle before opening the dura. The benefits are obvious: access to the lesion is improved, much less retraction is required as a result, and the brain is damaged less. Recovery from operation is thus more rapid and complete, and everyone concerned with these patients has been impressed by their easy convalescence. To see a patient sitting up in bed, with no œdema of the eyelids, and doing a crossword puzzle, the morning after the removal of a massive bifrontal meningioma together with its attachment to the falx and sagittal sinus, is a new experience in neurosurgery.

Bleeding.—Although urea makes operating easier and safer, paradoxically bleeding is increased in the early stages of operation. Two factors seem to be responsible. First and obvious is that, as the dura falls away from the skull when burr-holes and saw cuts are made, there is more venous bleeding from the dura in the space between it and the bone. This can be checked by pressure with gelatin foam, but we usually hitch up the dura to the pericranium at four or five points around the craniotomy, either at the beginning, or more often at the end, of the intradural procedure.

Secondly, more bleeding from small vessels in the scalp, dura, and brain seems to arise in the first twenty minutes or half-hour of operation than later. This is mostly arterial oozing, and is more of a nuisance than a danger. We have not found any defect in the hæmostatic mechanism, and we think that this kind of bleeding may be a result of the transient increase in blood-volume caused by the infusion of a hypertonic solution. This problem is being investigated further.

* A much more stable form of urea for intravenous use is now available commercially from Baxter Laboratories Ltd., 26, Great Tower Street, London, E.C.3.

No postoperative clots have formed after urea has been used. This is surprising, considering the factors mentioned above, and the slackness of the brain at the end of operation.

Lumbar C.S.F. Pressure

In a few patients we have studied the response of the lumbar C.S.F. pressure to urea administration. Although lumbar pressure is not always an accurate index of intracranial pressure, when the intracranial pressure is high the lumbar pressure is usually also raised. The effects of urea on the intracranial pressure should be reflected in a reduction of the pressure as determined by lumbar puncture. A typical response is shown in fig. 1. In this case an initial pressure of 180 mm. water dropped to −80 mm. at the height of diuresis two and a half hours after starting the infusion of urea. But the temporal relation between diuresis and fall in pressure is often less precise (fig. 2). (Indeed, to study the possible causal relation between pressure fall and diuresis, Javid and Anderson [1959] gave various hypertonic solutions, including urea, to monkeys before and after bilateral nephrectomy. After nephrectomy they found the fall in C.S.F. pressure was greater and better sustained than before nephrectomy. After excluding the relevance of the associated urinary diuresis Javid [1958] implicated the blood-C.S.F. barrier.)

The patient whose responses are recorded in fig. 1 was conscious throughout. His only significant subjective impressions were dryness of the mouth, which began with the diuresis, and mild frontal and occipital headache when his lumbar C.S.F. pressure was less than atmospheric.

Biochemical Changes

Diuresis begins shortly after the introduction of the urea, is at a maximum between half and three hours later, and continues at a diminishing rate for three to nine hours. As large quantities of urine may be excreted we insert a catheter into the bladder at the beginning of the infusion, and then release it hourly to avoid distension of the bladder.

The blood-urea level rises from the beginning of the infusion, and reaches its maximum at the end of the infusion. It falls slowly from that time, reaching normal in twenty to thirty hours. Values as high as 540 mg. per 100 ml. have been seen, without untoward clinical effects. But, because urea retention may be harmful, intravenous urea should not be given to patients with impaired renal function.

Toxicity

We have seen no major toxic effects. During the urea infusion 5 patients had rigors, but these ceased shortly after the infusion was stopped. In 3 cases we attributed the rigor to the fact that we had not allowed the solution to come to room temperature and because the rate of infusion was too rapid. In the other 2 the reaction was probably due to decomposition of the urea solution through age or improper storage. None of them showed any untoward result, and in particular there was no evidence of intravascular hæmolysis.

In a few arteriosclerotic patients Javid (1958) noted that the vein became prominent, distal to the needle, when a vein of the foot was used. We have noted similar local reactions, and occasionally in younger patients also. In some the vein has become very red and swollen both proximal and distal to the site of infusion, and in the conscious patient this may be painful. But the reaction has been shortlived, and has never progressed to thrombosis of the superficial and deep leg veins as in one of Javid's cases.

Local reactions were less frequent in the arm than the leg. With the patient recumbent slight elevation of the limb reduces the frequency of local venous irritation. The limb should be elevated only slightly—say by placing it on a pillow—so that at the point of entry of the needle the venous pressure is atmospheric or only slightly above. The proximal veins are then not fully distended. The flow is more rapid, and dilution of the urea by blood from other tributaries is more prompt.

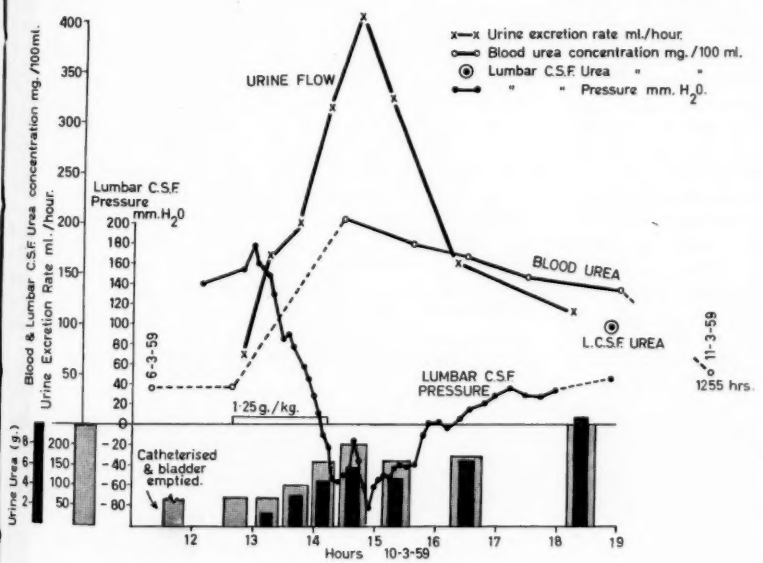

Fig. 1—Right frontal cystic glioma.

Lumbar C.S.F. pressure, blood-urea, urine-flow, and urea excretion after urea 1·25 g. per kg. body-weight by intravenous infusion.

Constancy of Effects and Diverse Uses

We have used intravenous urea in 102 intracranial operations for various pathological processes:

Glioma	26
Meningioma	12
Aneurysm	7
Lesions in and near the sella	14
Intracranial hæmatoma	3
Abscess	5
Trigeminal-root section	15
Posterior-fossa lesions	8
Miscellaneous	12

All cases showed obvious benefit, although this was sometimes more dramatic than others. Thus, the effect was less obvious in posterior-fossa lesions causing hydrocephalus than it was in lesions of the cerebral hemispheres; but, as one can almost always reduce the pressure by tapping a dilated ventricle, the need for urea is less in posterior-fossa tumours.

Apart from its use during operation, we think urea may have other important uses. One of these may best be illustrated

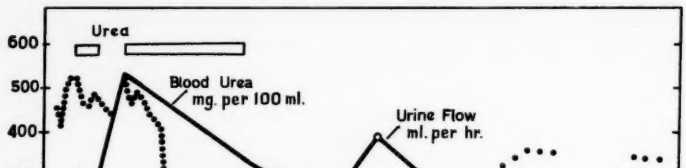

Fig. 2—Tuberculous meningitis.

Lumbar C.S.F. pressure, blood-urea, and urine-flow after urea 1·25 g. per kg. body-weight by intravenous infusion.

by observations on a patient who proved to have a right frontal glioma. He was admitted in coma, which had come on over thirty-six hours, and which had been deepened by exploratory burr-holes and aspirations. He was then given intravenous urea, and within an hour and a half he was conscious and rational enough to cooperate in a full examination. This pointed to the site of the lesion, which was then confirmed by angiography. Thus, urea may usefully tide over a comatose patient until he can be got into neurosurgical hands, and indeed it may keep him going until operation can be arranged. We have seen its benefit in 6 such cases. Incidentally its effect lasts longer than that of other hypertonic solutions, and there is little of the " rebound " in pressure which often follows their use. Thus, it might be used safely to prepare a patient for an ambulance journey from an outlying hospital to a neurosurgical centre.

We have also used urea with dramatic effect in what our American colleagues call " the second-day slump ". This happens in patients who are very well the day after craniotomy. On the second day they become drowsy—sometimes comatose—and may develop neurological signs referable to the operation site (e.g., hemiplegia or aphasia). The safe assumption is that a clot has accumulated. This requires re-elevation of the bone-flap, and inspection of the operative site; but more often than not, no significant clot is found, the brain only appearing slightly swollen. Such patients usually recover, but they can cause much anxiety. In one such case when we tried intravenous urea, the patient became fully conscious and was without neurological deficit by the time the infusion was completed. This state lasted for about eighteen hours, when he again became drowsy. This time a half dose of urea was given, again with prompt recovery, which persisted.

Head injuries—We have used urea in 22 cases of acute head injury in which the brain was " tight ", after sizeable clots had been excluded by multiple burr-holes or craniotomy. Once, at operation, the effect was as dramatic as described above, but the patient's condition did not improve correspondingly. He did make a good recovery eventually, although it would be difficult to deny that he might have done so without urea. This is a common difficulty in evaluating the " medical " treatment of head injuries—e.g., with hypothermia or dehydration. But if the intracranial pressure is known to be high, if sizeable clots have been excluded, and if urea is known to be safe (as we believe it to be in these circumstances), it seems reasonable to try it.

Tuberculous meningitis.—We have used urea in 3 cases of tuberculous meningitis in which increased intracranial pressure seemed to demand some kind of decompression procedure.

Fig. 2 records its effect in a 23-year-old woman who was admitted to the tuberculous-meningitis unit with a proven infection. The striking clinical feature was bilateral papilloedema. Treatment with intrathecal streptomycin was started, but she continued to have severe headache, the lumbar C.S.F. pressure rose, and the papilloedema increased. An air-encephalogram indicated obstruction by basal exudate; hence a course of intrathecal tuberculin was started. While her general condition remained the same, the C.S.F. pressure continued to rise to about 500 mm. water, fresh retinal hæmorrhages appeared, and the visual acuity, which had been J.1 bilaterally, dropped to J.16 in the right eye and J.2 in the left. At this stage urea was given intravenously, and then it was continued orally (vide infra) for forty-eight hours. The lumbar pressure fell, no further changes appeared in the retinæ, and the visual acuity returned to normal. A week later the lumbar pressure again rose to 500 mm., but it was reduced to normal with urea given by mouth. The patient later recovered satisfactorily, with normal vision.

Urea was beneficial in the 2nd patient, but not in the 3rd, who was critically ill with tuberculous meningitis, and showed evidence of ventricular and subarachnoid bleeding.

Benign intracranial hypertension (otitic hydrocephalus).—In 2 patients with this affection urea has brought about a prompt and striking reduction in the lumbar C.S.F. pressure; but, as they were both in good general condition and had only moderate papilloedema with no reduction in visual acuity, we did not consider further treatment necessary. Urea might be useful in patients with pronounced papilloedema and failing vision, for whom surgical decompression is usually advised. In such cases, the oral route might be preferable to repeated intravenous infusions. Javid (1958) has shown that urea is effective when given by mouth in doses comparable to those given intravenously. Urea crystals can be dissolved in water. We have found the following mixture reasonably palatable: urea, 300 g.; simple syrup, 150 ml.; syrup of orange, 150 ml.; and water to 1000 ml. Such solutions should be stored at 2–8°C and should not be used after seven days from their preparation. The total daily dose of 1–1·5 g. per kg. body-weight is divided into three and taken eight-hourly. It has an unpleasant taste, and sometimes causes vomiting, which if persistent may necessitate discontinuing treatment by this route. But when urea can be taken by mouth the patient is also spared discomfort from local reaction in the vein used for infusion. Furthermore, in the conscious patient the rapid reduction in pressure accompanying intravenous infusion may cause much headache.

Contraindications

As noted above, urea should not be used in patients with impaired renal function. On admission we examine the urine and determine the blood-urea, and, if these are normal, we have no hesitation in using urea. The youngest patient was two years old, and the oldest seventy-two.

Because the tendency to increased bleeding already mentioned may contraindicate the use of urea, we doubt whether it has a place in the treatment of acute subarachnoid or intracerebral hæmorrhage, except as an immediate

preoperative measure. Until more is known about its mode of action and effects, we advise against its indiscriminate use in acute head injuries in which the pathology is not certainly known.

Comparison with Pressure-reduction by Controlled Respiration

We have too little experience of controlled respiration to make a useful comparison, but our impression from 5 recent cases is that controlled respiration considerably reduces the vascularity of the scalp, dura, and brain, and in this respect is superior to urea. Its pressure-reducing effect, however, is much less than that of urea. In 11 further cases we have combined the two procedures. This may indeed be the ideal combination, and there seems to be no theoretical or practical objection.

Mechanism of Action

Any theory of mechanism must explain the following:

1. The reduction in C.S.F. pressure; and, when the skull is opened, the reduction in volume of the intracranial contents.
2. Why urea, on an equiosmolar basis, produces a more protracted and profound effect than other hypertonic agents.
3. The absence of a secondary rise in pressure (a rebound phenomenon), such as often occurs after giving sodium chloride.

Weed and McKibben (1919) argued that hypertonic agents generally act by reducing principally the brain bulk rather than the C.S.F. volume or the intracranial blood-volume. They suggested that the brain bulk is diminished by water loss: as long as the concentration of the agent is higher in the blood than in the brain there is an osmotic gradient favouring the passage of water from brain to blood. The less readily a substance passes from blood to brain the longer will this osmotic gradient be maintained, and the greater will be the transfer of water. If a substance enters the brain much less readily than it enters other soft tissues (i.e., a blood-brain barrier effect), then, when given intravenously in hypertonic solution, it will selectively dehydrate the brain.

The reduction in brain bulk is obviously much greater than that of other soft tissues of comparable water content, and we think that a barrier to the entry of urea into the brain best explains our clinical observations. We suggest that urea is more effective than other agents because it enters the brain more slowly.

Davson (1956) in a discussion of the mode of action of hypertonic agents, emphasises the significance of a barrier effect, but he does not distinguish between the relative importance of the blood-brain barrier on the one hand and the blood-C.S.F. barrier on the other. When considering specifically the mode of action of hypertonic urea, Javid (1958) implicates the blood-C.S.F. barrier.

We feel that the following clinical observations support Weed and McKibben's belief (1919) that the blood-brain exchanges are relatively more important:

1. Urea is less effective in patients with much hydrocephalus, in whom there is relatively more C.S.F. and a smaller brain-volume than normal.
2. Urea is effective in reducing brain bulk during craniotomy in patients with diffuse and severe cerebral swelling due to trauma. At the time of giving urea little intracranial C.S.F. could have been available for reabsorption.
3. If urea is given during craniotomy to patients in whom continuous ventricular drainage has first been established, then the volume of the intracranial contents is reduced very much further.

Little is known about the rate of entry of urea into the brain relative to its entry into other soft tissues. Only two in-vivo studies have been reported.

That by Riser et al. (1938) suggests that urea diffuses into the brain almost as rapidly as it does into muscle, and that at high urea levels the urea concentration in both brain and muscle approaches that of plasma. Conway and Fitzgerald (1942) on the other hand, provided more definite evidence in favour of a barrier to urea. They showed that urea enters the brain much more slowly than it enters muscle. Both groups of investigators found that at equilibrium at normal urea levels the brain contains significantly less urea than the plasma. But because in both studies the observations were few, such experiments must be repeated.

In-vivo rather than in-vitro studies are necessary as the blood-brain barrier presumably depends upon the integrity of the normal in-vivo anatomical relation between plasma in the capillary lumen and the brain substance. Thus, Coxon's report (1957) on the free entry of urea into isolated guineapig brain slices is not relevant to this study.

As to the nature of the barrier, a simple physical obstruction to free diffusion is one possibility. Such an obstructive barrier would almost certainly retard the exit of urea from the brain as much as it would delay the entry. Thus, as urea is excreted by the kidneys and the plasma level falls, one would expect the brain-urea concentration to exceed that of the plasma-urea until equilibrium is again reached at normal urea levels. During this interval the osmotic gradient would favour the passage of water from plasma to brain, producing a rebound rise in pressure. We have not seen such a secondary rise in pressure after giving hypertonic urea to our patients, nor have we seen this in the few cases in which we have made extended manometric studies. More probably the barrier to urea is an energy-consuming metabolic process, and urea is actively " pumped out " of the brain as the plasma level falls.

The mechanism requires further study, for it has obvious importance, theoretical and practical. We are now engaged in experiments designed to test this barrier hypothesis.

Summary

In 129 neurosurgical patients intravenous urea was used to reduce the intracranial pressure. The main effect was a decrease in brain bulk, which made operation easier and safer. Although arterial oozing was often increased in the early stages of operation, this was more of a nuisance than a danger. The fall in intracranial pressure was measurable at lumbar puncture.

No major toxic effects arose. Local reactions were noted in the vein used, but they never progressed to thrombosis. The blood-urea level rose and diuresis began shortly after the infusion was started; hence urea should not be given to patients with impaired renal function.

Apart from its use during brain operations urea may serve (1) to tide over a comatose patient until he can be got to a neurosurgical centre; (2) for treating " the second-day slump "; (3) for cases of acute head injury or tuberculous meningitis in which the intracranial pressure is high; and (4) for relieving benign intracranial hypertension.

The most likely mechanism of the reduction of intracranial pressure is by means of a blood-brain barrier to urea.

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DIAGNOSIS AND TREATMENT OF VASCULAR INSUFFICIENCY CAUSING PERCEPTIVE DEAFNESS

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GREAT advances have been made in the prophylaxis and treatment of conductive deafness. Perceptive deafness, on the other hand, has been regarded as unamenable to any treatment. The patient with perceptive deafness seldom hears well with a Medresco hearing-aid; and manufacturers have undertaken a great deal of research in an effort to help them.

An analysis of all cases of deafness over a period of six years in this rural area of Northern Ireland reveals that perceptive deafness (including presbyacusis) is almost as common as conductive deafness. The figures for conductive deafness have tended to decrease every year, but those for perceptive deafness have remained steady or increased slightly. The efficacy of modern prophylaxis of conductive deafness, the increasing average age of the population, and the effects of acoustic trauma will inevitably raise the proportion with perceptive deafness.

The objective of this study was to establish a means of alleviating symptoms and preserving function in perceptive deafness.

Clinical Material

The investigation covered 981 cases of perceptive deafness seen in the six years 1953–58. Deafness was due to the following causes: congenital deafness (50), virus deafness (27), traumatic labyrinthitis (6), acoustic and head trauma (31), and senile deafness (390)—504 cases in all. The remaining 477 cases were of perceptive deafness without known cause. Of these, investigation was considered to be inadequate in 160, leaving for consideration 317 (175 in males and 142 in females).

Findings

The following were apparently significant: (1) age, (2) mode of onset, (3) presence or absence of vertigo, (4) presence or absence of fluctuation of the hearing level, (5) the effect of increase in blood-supply to the affected ear.

Age.—A purely arbitrary age of 40 years was taken and each case was placed in the under-40 or over-40 age-group. Of the 317 patients, 106 were under 40 and 211 were over 40.

Mode of onset.—Two modes of onset were recognised—sudden (i.e., deafness coming on in hours or days) and gradual. The onset was sudden in 73 cases and gradual in 244 cases.

Vertigo.—135 patients had vertigo (observed or recorded in the history) and 182 had no vertigo.

Fluctuation of hearing level.—Each patient was specifically asked about such fluctuation, which was present in 122 cases and absent in 195 cases.

Increase in blood-supply to affected ear.—This was effected by blocking the sympathetic chain at or above the stellate ganglion. In all cases an audiograph was done before and thirty minutes after the injection. If hearing improved it did so in most cases within this period, but in a few cases improvement was delayed for several hours or more. Any definite improvement in hearing, manifest within twenty-four hours of the injection, was attributed to the injection. Hearing was thus improved in 85 cases and unimproved in 232 cases.

TABLE I—DURATION OF DEAFNESS RELATED TO FLUCTUATION IN HEARING AND RESPONSE TO SYMPATHETIC BLOCK IN 271 PATIENTS WITH DEAFNESS OF KNOWN DURATION

Duration of deafness (yr.)	Fluctuation		Response to sympathetic block	
	Present	Absent	Positive	Negative
Less than 1	52 (51%)	50	37 (36%)	65
1–5	32 (47%)	36	19 (28%)	49
Over 5	24 (24%)	77	19 (19%)	82

In fig. 1 age is related to mode of onset, vertigo, fluctuation in hearing level, and effect of sympathetic block. Sudden onset is slightly commoner in the younger age-group, and vertigo in the older; whereas fluctuation in hearing level and the effect of sympathetic block are unrelated to age.

In table I duration of deafness is related to fluctuation in hearing level and response to sympathetic block. The table shows that, the shorter the history, the more likely is fluctuation and the more likely is hearing to be improved by sympathetic block.

In fig. 2 sudden onset is related to vertigo, fluctuation of hearing level, and response to sympathetic block; in fig. 3 vertigo is related to fluctuation in hearing level and response to sympathetic block; and in fig. 4 fluctuation in hearing level is related to response to sympathetic block. In table II sex is related to the other factors.

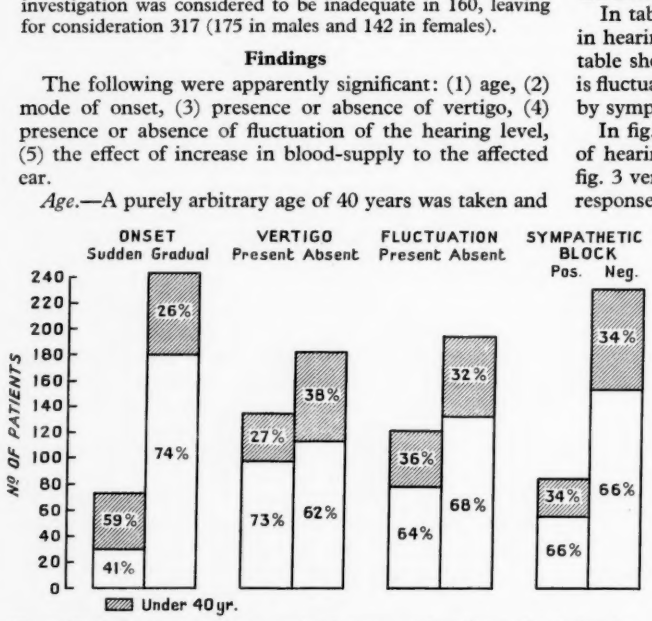

Fig. 1—Patients' ages related to mode of onset, vertigo, fluctuation in hearing level, and effect of sympathetic block in 317 cases of perceptive deafness.

Clearly patients with fluctuation in hearing level are more likely to have vertigo; a positive response to sympathetic block is much commoner in patients with both vertigo and fluctuation (figs. 3 and 4); and fluctuation in hearing level and improvement in hearing after sympathetic block are commoner in males than in females (table II).

It is apparent that early cases of fluctuating deafness with vertigo should respond best to measures designed to increase the labyrinthine circulation: this is the "reversible group" (Wilmot 1957).

Ætiology

The factors producing perceptive deafness are usually described under two headings—

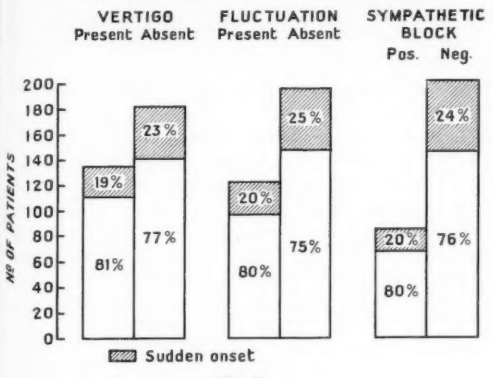

Fig. 2.

Fig. 2—Mode of onset related to vertigo, fluctuation in hearing level, and effect of sympathetic block.

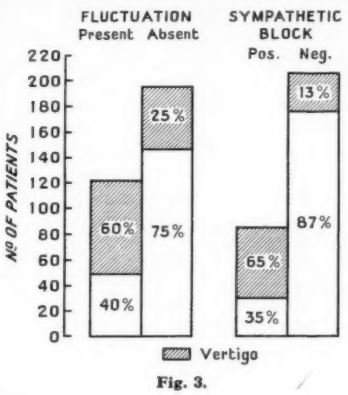

Fig. 3.

Fig. 3—Vertigo related to fluctuation in hearing level and effect of sympathetic block.

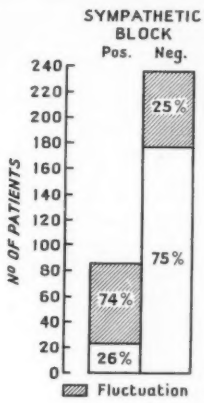

Fig. 4.

Fig. 4—Fluctuation in hearing level related to effect of sympathetic block.

congenital and acquired. Of the congenital group, heredity and rhesus incompatibility are the most important. In the acquired group maternal illness or malnutrition during pregnancy, neonatal illness or malnutrition, acute infections, especially in childhood (particularly mumps, influenza, and meningitis), acoustic trauma, head injury, hypertension, hypothyroidism, drugs, Caisson disease, eighth-nerve tumours, and ageing have all been implicated.

We believe, as does Simpson (1949), that in the vast majority of cases vascular insufficiency is an important

TABLE II—RELATION OF SEX TO OTHER FACTORS

Factor	Female (%)	Male (%)
Under 40 years	22	22
Sudden onset	33	33
Vertigo	41	43
Hearing improvement with sympathetic block	22	30
Fluctuation of hearing	22	38

underlying cause and that other factors have played no significant part. Moreover we believe that in certain types of perceptive deafness (especially typical, Ménière's disease and sudden perceptive deafness in young people) the commonly associated psychological element of emotional tension and anxiety exists before the onset of symptoms, thus constituting another important ætiological factor. In progressive deafness without fluctuation, this does not appear to apply to the same extent.

Clinical Features

Deafness

In the common type of perceptive deafness, with or without vertigo, the onset of deafness is gradual. Very often there is an intermittent loss of hearing, and thus the patient and his doctor may not realise its seriousness. Such patients presenting themselves for the first time may be found to have normal, or almost normal, hearing in both ears; but on repeated examination their hearing will be found to fluctuate; they are usually well able to appreciate their own powers of hearing on any given occasion. These fluctuations of hearing are often incorrectly assigned to nasal catarrh or eustachian obstruction. One reason for this mistaken idea may be that periods of increased deafness are apparently linked with environmental cold and with upper-respiratory-tract infections, and many patients find that they are better in the summer than the winter. One patient stated that he could regularly induce an attack of labyrinthine vertigo with increased deafness and tinnitus by drinking a glass of cold water.

Initially, in patients with fluctuating hearing loss, long periods of normal hearing are interspersed with shorter periods of impaired hearing. Later the periods of impaired hearing become longer and longer, and finally perceptive hearing loss is constant and severe. Whereas in old age the common type of perceptive deafness is predominantly a *high-tone loss*, in the young or middle-aged adult seeking early advice the common type is a *low-tone loss;* when high-tone loss occurs in this group it is usually constant from the onset without any periods of improved or normal hearing.

In other cases, usually in healthy young adults, the onset of deafness is alarmingly sudden. Though usually unilateral, the deafness can come on simultaneously, or almost simultaneously, in both ears, and it is usually accompanied by vertigo, which may be severe. In some cases a loud sound close to the ear seems to have precipitated the onset. In this type of deafness the loss of hearing is usually profound and may be total and permanent. Sometimes, however, there is gradual but incomplete recovery during the ensuing week or ten days; recovery rarely continues after this time (Wilmot 1959).

Sudden perceptive deafness associated with mumps and other systemic infections is also often complete and permanent, but is seldom accompanied by vertigo.

Tinnitus

The type and tone of the tinnitus are very variable and have seemed of little help to us in investigating this disorder. The intensity of the tinnitus usually accords closely that of the deafness. Some patients are much more obsessed by their tinnitus, others by their hearing loss or vertigo. When tinnitus is the only complaint, slight hearing loss on the affected side is usually found by pure-tone audiometry.

Vertigo

The vertigo may, like the tinnitus, vary; but types and grades of vertigo can be distinguished more easily. Vertigo has been defined as " an hallucination of movement of the patient in relation to his environment " (Cawthorne 1952), and this may be quite apparent to an intelligent patient; but others may have difficulty in

analysing things so clearly and may confess merely to feeling " dizzy ", " giddy ", or " light-headed ".

In a severe attack of labyrinthine vertigo the onset may be sudden or gradual. Sometimes the onset is so sudden that the patient falls to the ground and may even injure himself in so doing. Vomiting may be severe and prolonged, or the patient may have only nausea. Spontaneous nystagmus may be observed. Both deafness and tinnitus are often increased shortly before and during the period of vertigo. The duration of the attack is very variable and is not necessarily related to its severity.

Other Symptoms

These are common when looked for. The majority of patients with an early inner-ear disorder have other head symptoms. Genuine migraine may occur on the same side of the head, but is not so common as a feeling of fullness on the affected side: this is often described as " a stuffed-up feeling " or " a cotton-wool feeling "—one patient with bilateral ear symptoms said he often felt as if he had a cap on his head when he had not.

Hearing may be distorted; and this is characteristically an early symptom. It is complained of most frequently by women and young people, who have greater opportunity to note it since they are often subjected to children's voices and loud music.

We have also seen cases with gustatory sweating on the same side of the face as the deafness and tinnitus.

Cold hands and feet and chilblains with evidence of acrocyanosis are common in the younger female patients with inner-ear symptoms.

Diagnosis

In the past there has been considerable bias towards diagnosing middle-ear deafness in any case where no obvious cause for deafness was present. The first essential in the diagnosis of perceptive deafness is to exclude middle-ear deafness. An accurate history, a simple clinical examination, and audiometry are usually all that is required, but where doubt persists other tests are necessary.

In taking a history all the features of perceptive deafness should specifically be inquired into: duration; variability; mode of onset and subsequent course of the deafness; and presence or absence of tinnitus, vertigo, or hearing distortion; the state of the general and peripheral circulation; other head symptoms, including migraine; relation to anxiety or grief; relation to external temperature; influence of nasal disorders, particularly head colds; vasomotor symptoms; the possibility of acoustic trauma; the family history; the previous history; the influence of surroundings—all may provide useful information and point towards conductive or perceptive deafness.

In the doubtful case bone-conduction audiometry is useful, but insert masking must be used when the hearing loss is unilateral. The pneumatic speculum and inflation of the eustachian tubes will help further. Eustachian inflation should be done with the routine use of the nasopharyngoscope, and the hearing tested audiometrically before and after inflation. Under these circumstances it is quite easy to show whether obstruction is, or is not, present and whether inflation has produced definite hearing improvement or not.

True aural vertigo with perceptive deafness, associated with hypotension or normotension, characteristically gives an asymmetrical hearing pattern; whereas perceptive deafness associated with hypertension (and often also with vertigo) usually produces a symmetrical pattern in the hearing of the two ears.

Except in the case of explosive damage to one ear, acoustic trauma also usually produces symmetrical hearing curves; and this is true, too, of occupational deafness (previous occupations may be of more significance than the present one).

Psychogenic deafness or malingering can usually be detected quickly by a skilled team. Consecutive audiograms are dissimilar, and the audiometric findings do not fit in with the clinical picture.

It is essential that in all cases of unilateral perceptive deafness the cranial nerves be tested, a recruitment test and caloric tests done, and X-ray examination of the internal auditory meati undertaken, if indicated, to exclude a neurofibroma of the eighth nerve.

In bilateral and unilateral cases the blood-pressure should be recorded and the optic fundi and peripheral vessels examined for evidence of vascular disease.

Smoking habits should be inquired into and recorded. Heavy cigarette-smoking, although not perhaps of the same significance as in thromboangiitis obliterans, can adversely influence the progress of the disease.

Incomplete congenital deafness may present difficulty in diagnosis, if the patient is first seen in adolescence or early adult life. The initial interrogation of the patient or relative is therefore important.

Premature senile deafness seldom comes on before the age of 50 and is usually accompanied by other stigmata of ageing. The audiometric pattern, with symmetrical high tone-loss preponderating, is similar to that of presbyacusis coming on in old age.

If the precise nature of the perceptive deafness is still obscure, special diagnostic procedures may help in differential diagnosis.

Sympathetic Block

Just as eustachian catheterisation and the Rinne test are used routinely in the investigation of midde-ear deafness, we believe that the sympathetic fibres supplying the inner ear should be blocked as a routine test in certain cases of perceptive deafness. If tinnitus and other subjective sensations are relieved and there is objective evidence of hearing improvement, this suggests that the induced vasodilatation has improved function and that the case is still in the reversible stage. This improvement may be almost immediate or it may be delayed for several hours or days, and it is usually greatest when sympathetic release—evidenced by Horner's syndrome and flushing of the tympanic membrane—is greatest. It may last for a few hours only or persist indefinitely. Improvement after sympathetic block does not occur in senile deafness, acoustic trauma, occupational deafness, or deafness associated with hypertension: in fact, in this last disorder there is often a definite fall in the audiograph.

Recruitment Test

The binaural or loudness balance test is a valuable confirmatory test of end-organ damage and should be done whenever possible, but it is not infallible. It cannot be done when the difference between the hearing loss is maximal, or minimal, and is ideal when there is a 40–50 db. difference between the ears at frequencies 1000–4000 c.p.s. We have not found the monaural test of any value.

Positional Tests

These tests can be carried out quickly as a routine procedure or more deliberately using electrical nystagmography. Often a good history will give prior indication of the results of these tests. Where there is considerable

vertigo but little deafness, these tests are of value in revealing damage to the static labyrinth.

Caloric Tests

All cases of perceptive deafness with vertigo should have these tests done. Water at 30 C and 44 C has been used, and the results recorded electrically, for the past two years. These tracings form permanent records—a great advantage over the usual methods of recording, since they can be filed and compared with other tracings.

Management

It seems likely that, in addition to a " constitutional factor " (i.e., the patient's " make-up " conditioned by heredity, neonatal environment, emotional and physical experiences, smoking habits &c.) there is a " precipitating factor " such as infection, cold, or sudden stress. If this is correct, physical treatment, although very important, is only part of the management. The otologist must have the closest possible cooperation of the family doctor and know as much as possible of his patient's background.

In young normotensive patients the onset of the symptoms is often dramatically sudden; in such cases the response from the doctor responsible for treatment should be equally brisk, for delay in such cases may be disastrous so far as hearing is concerned.

Patients presenting after many months or years of symptoms are often found to have permanent irreversible damage. In this type of case treatment should be directed towards preserving the remaining function rather than trying to restore normal function—although exceptionally improvement may occur in spite of a long history.

In older patients with genuine inner-ear symptoms the clinical picture is often obscured by hypertension. These symptoms often resolve when the hypertension is under control.

Obviously the patient with early symptoms—which must not be dismissed as functional—has the best prognosis. The damage to the cochlea and vestibule is reversible initially in virtually all cases. This reversibility may last for a very short time, possibly as little as four hours with severe vascular occlusion; or it may persist much longer, for years in some cases where vascular occlusion is intermittent and incomplete. Success in treatment must depend therefore largely on the physician's ability to assess the degree of reversibility and his ability to do this *early* in each individual case. Whereas it has long been recognised by many that anxiety symptoms are the rule in patients with typical Ménière's disease, it is not generally appreciated how often these symptoms have been present *before* the establishment of deafness, tinnitus, and vertigo. We believe that the majority of inner-ear disorders of the " Ménière " type are " tension " phenomena, and that it is possible to predict from early symptoms that a patient will develop a fully fledged Ménierè's syndrome if untreated.

Treatment

Early cases with slight (10–20 db) low-tone unilateral deafness and tinnitus.—Intelligent interest in the patient's symptoms, thorough investigation, firm reassurance, simple sedation, and a promise of help should the need arise may be all that is required. If deterioration occurs despite these measures, vasodilator therapy is indicated.

Sudden onset of severe vertigo with tinnitus and unilateral deafness in a previously healthy normotensive patient.—The acute attack should be treated by *immediate* stellate block followed by large doses of vasodilator drugs (e.g., 30–40 mg. or more of ' Perdilatal ' daily, if necessary by the intramuscular route). Stellate block can be repeated as indicated by the patient's clinical and audiometric responses—it is more effective in the acute attack than vasodilators alone. Once the severe vascular spasm has been relieved, oral vasodilator therapy (especially with perdilatal) often controls the condition. Heavy sedation is not necessary if this treatment is applied efficiently.

Similar treatment should be applied where sudden deafness develops with little or no coincident vertigo (Wilmot 1959). In both these classes of case, maintenance therapy with vasodilators may be indicated for the commonly associated acrocyanosis.

Cases with 20–30 db or more loss of hearing and a history of from several weeks to a few months.—Here a stellate block should be done as a diagnostic procedure under audiometric control. It often causes a dramatic reduction in, or disappearance of, the tinnitus and head symptoms and sometimes improves the hearing. Again, vasodilator therapy should follow and be continued for at least a month. Symptoms are often reduced by prolonged vasodilator therapy alone.

Cases in which the above measures have given some relief but have failed to check the progress of the condition.—Repeated stellate block with intensive oral vasodilator therapy (up to 48 mg. perdilatal daily) is occasionally successful in this type of case, but cervical sympathectomy is more economical of time and effort and more sure in its results. Partial, occasionally complete, recovery of hearing and complete recovery of equilibration is common in this group.

Sympathectomy is also indicated in the following conditions:

1. When the patient has already a critical loss of hearing in one ear and the hearing in the good ear is progressively dropping.
2. When the patient is deaf in one ear and has had an episode of temporary perceptive deafness in the good ear.
3. When treatment has prevented further hearing loss on one or both sides, but failed to prevent continued incapacitating vertigo.
4. Where there is a strong indication for sympathectomy on one side, we consider it best to operate on the other side also if there is any reasonable hope of restoring function or diminishing further loss of function. This will usually depend largely on the age of the patient and the length of the history.

Cases which have had persistent severe deafness and tinnitus for a relatively long period with incapacitating vertigo.—Palliative therapy with sedatives, antihistaminics, or vasodilators may give some symptomatic relief in this group, and intelligent management may obviate the need for surgical destruction of the labyrinth, which we have done very rarely since our experience of other forms of treatment has grown.

Other traditional measures.—We have been unable to convince ourselves that any benefit whatever results from low-salt or low-fluid diets. The use of barbiturates, tranquillisers, and antihistaminic drugs before investigation is complete may invalidate audiometric and, particularly, caloric responses. Their use should therefore be reserved for treatment after an exact diagnosis has been made. It seems likely that tranquillisers may prove to be more valuable than the barbiturates.

Summary

A study of 317 cases of perceptive deafness, with and without vertigo, has shown that vascular insufficiency of the labyrinth is an important ætiological factor.

In early cases this condition is often reversible if the appropriate treatment is applied. In more advanced cases some prospect of improving function now exists.

Vasodilators are of considerable value in certain types of perceptive deafness; but they should be used discriminatingly, and only after adequate investigation and when results can be checked by audiometry.

This investigation would not have been possible without a generous grant to one of us (T. J. W.) from the Northern Ireland Hospitals Authority. We are also grateful to Mrs. K. Whelan, research technician in 1957–58, for her careful preparatory work; to Mr. Duncan M. Cheyne for the diagrams and statistical work; and to the directors of the Ferens Institute of Otolaryngology, Middlesex Hospital, for generous facilities.

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URINARY ŒSTROGENS AFTER ENDOCRINE ABLATION

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DRAMATIC improvement in the clinical course of metastatic breast cancer in women may result from removal of the ovaries, adrenals, or pituitary gland. The mechanism of this response is obscure and recent investigations suggest that it is not related to alterations in the excretion of those œstrogens which can be estimated chemically in the urine (Strong et al. 1956, Bulbrook et al. 1958a, b, and c). We now report a further study in which œstriol, œstrone, and œstradiol-17β have been estimated in the urine of patients with breast cancer before and after oophorectomy, adrenalectomy, and radioactive implantation of the pituitary (Forrest et al. 1959).

Methods

The patients studied were women with inoperable or metastatic breast cancer treated by endocrine surgery. Women of premenopausal years were treated in the first instance by removal of the ovaries only, adrenalectomy and pituitary implantation being reserved for those who failed to respond to this simpler measure or those in whom relapse followed initial benefit. Postmenopausal women were treated initially either by adrenalectomy plus oophorectomy or by destruction of the pituitary with radioactive implants. Response to these forms of therapy was judged on an objective basis, and improvement was accepted only when there was visible or radiological evidence of regression of tumour deposits.

Urine was collected for œstrogen estimations while the patients were in hospital and taking a normal diet.

Aperients known to give rise to abnormal pigments were not allowed. The urine was collected in 3-day pools from which duplicate aliquots of 200 ml. were used for analyses. No steroid therapy was given during the preoperative or post-oophorectomy estimations, but after adrenalectomy and pituitary implantation the patients were given maintenance therapy of cortisone 50 mg. per day. In ten adrenalectomised patients the collections were made on the last 3 days of a 5-day period when 120 units corticotrophin gel was given daily. These estimations have been differentiated in the figures by the letter C.

TABLE I—MAGNITUDE OF ERROR IN A RANDOM SERIES OF ŒSTROGEN ESTIMATIONS

Œstrogens	No. of duplicate analyses	Mean excretion (μg. per 24 hours)	Mean difference between duplicates (μg. per 24 hours)
Œstriol ..	27	2·77 ± 1·54*	0·26 ± 0·25*
Œstrone ..	16	1·79 ± 0·67*	0·22 ± 0·23
Œstradiol-17β	12	1·55 ± 0·90*	0·17 ± 0·24

* Standard deviation.

Although in most patients the estimations were carried out within 1 month of endocrine surgery, all those within 6 months have been included in the postoperative results provided that during this time the response of the patient and the maintenance therapy did not change. Where several estimations were carried out on any one patient the mean value during the first 6 months after surgery has been used.

The method of estimating œstriol, œstrone and œstradiol-17β was that of Brown (1955).

After acid hydrolysis of the urine the œstrogens were extracted by ether and fractionated by benzene-petroleum ether partition followed by methylation and chromatography of the methyl ethers on alumina. Quantitative estimations of each fraction were made by the Kober colour reaction and the results calculated in microgrammes per 24 hours. Any fraction containing an abnormal pigment was discarded. In this laboratory recovery figures of over 80% of added œstrogens to acid hydrolysed female urine have been consistently obtained and the error between duplicate analyses has been within satisfactory limits (table I).

TABLE II—PREOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY PLUS OOPHORECTOMY AND BY RADIOACTIVE IMPLANTATION OF PITUITARY

Response of cancer		No.	μg. per 24 hours			
			Œstriol	Œstrone	Œstradiol	Total
Ax	Benefit	8	4·2 ± 0·95	1·2 ± 0·36	0·7 ± 0·36	6·1 ± 1·39
	No benefit	7	4·1 ± 0·86	1·9 ± 0·5	0·8 ± 0·5	6·8 ± 1·41
Hx	Benefit	9	4·2 ± 0·56	1·8 ± 0·49	0·48 ± 0·25	6·4 ± 1·12
	No benefit	16	5·0 ± 0·69	1·5 ± 0·31	0·33 ± 0·23	6·9 ± 0·80

Ax = adrenalectomy + oophorectomy. Hx = pituitary implantation.

TABLE III—PREOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY AND OOPHORECTOMY

Response of cancer	No. of patients	Mean excretion of œstriol, œstrone, œstradiol	
		μg per 24 hours	log μg per 24 hours
Benefit ..	8	6·1 ± 1·39*	0·671 ± 0·124
No benefit	7	6·8 ± 1·41	0·734 ± 0·130
Mean difference		0·7 ± 1·99	0·063 ± 0·181
P		> 0·7	> 0·7

* Standard error of mean.

TABLE IV—PREOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY PITUITARY IMPLANTATION

Response of cancer	No. of patients	Mean excretion of œstriol, œstrone, œstradiol	
		μg. per 24 hours	log μg. per 24 hours
Benefit ..	9	6·4 ± 1·12	0·751 ± 0·085
No benefit	16	6·9 ± 0·80	0·772 ± 0·069
Mean difference		0·5 ± 1·48	0·021 ± 0·122
P		> 0·7	> 0·8

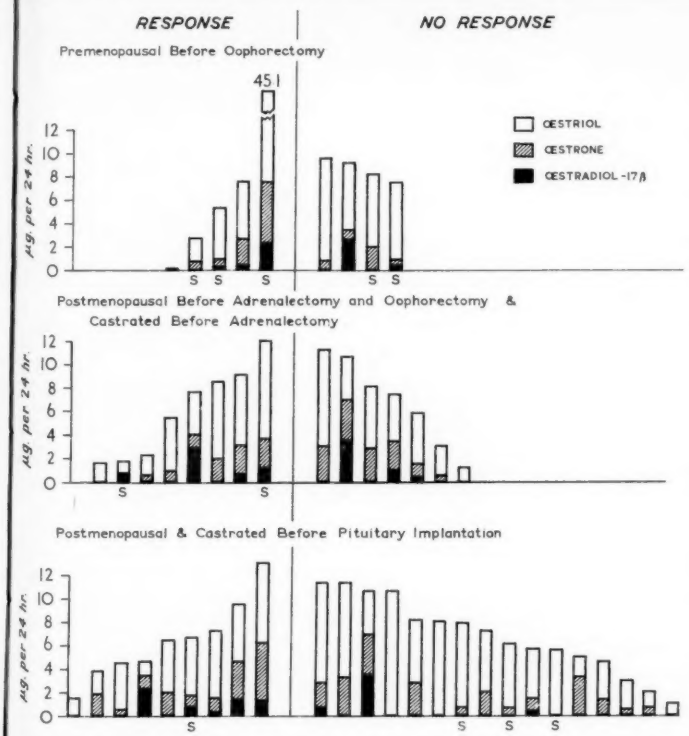

Fig. 1—Preoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of 39 patients with breast cancer treated by endocrine ablation.

S = modified method of Brown et al. (1957)

More recently the additional purification step introduced by Brown et al. (1957) has been used in the estimations.

This modification reduces interference by cortisone metabolites and may increase the recovery of œstrogens when maintenance therapy is being taken. Analyses in which the modified method was used have been designated by the letter S in the figures. For practical purposes we regard the lower limit of sensitivity of these methods as 1 μg. of each œstrogen fraction per 24 hours.

Results

Preoperative Estimations

The excretion of œstriol, œstrone, and œstradiol-17β was estimated in one or more 3-day pools of urine in thirty-nine women with breast cancer before endocrine surgery, several of whom were treated by more than one method of endocrine ablation. In fig. 1 the results have been arranged in three groups: (1) estimations in premenopausal women before oophorectomy, (2) estimations in castrated and postmenopausal women before adrenalectomy or adrenalectomy plus oophorectomy, and (3) estimations in castrated and postmenopausal women before pituitary implantation. It is clear that the response to endocrine surgery bears no relation to the preoperative levels of the three œstrogen fractions.

The means of the arithmetic and logarithmic values of œstrogen excretion before adrenalectomy and before pituitary implantation in responding and non-responding patients are compared in tables II–IV. The mean œstrogen levels in those patients whose cancer regressed did not differ significantly from those in whom no improvement occurred.

Postoperative Estimations

The excretion of the three œstrogen fractions was also estimated in one or more 3-day pools in fifty women with breast cancer after endocrine surgery. The results, which are arranged in an identical way to those before operation, again show no significant relation to the response to oophorectomy, adrenalectomy, or pituitary implantation (fig. 2; tables V–VII). Comparison of the results after adrenalectomy plus oophorectomy and pituitary implantation indicates that significantly lower values follow the former operation (table VIII).

Preoperative and Postoperative Estimations

Estimations of urinary œstrogens were carried out in ten postmenopausal patients

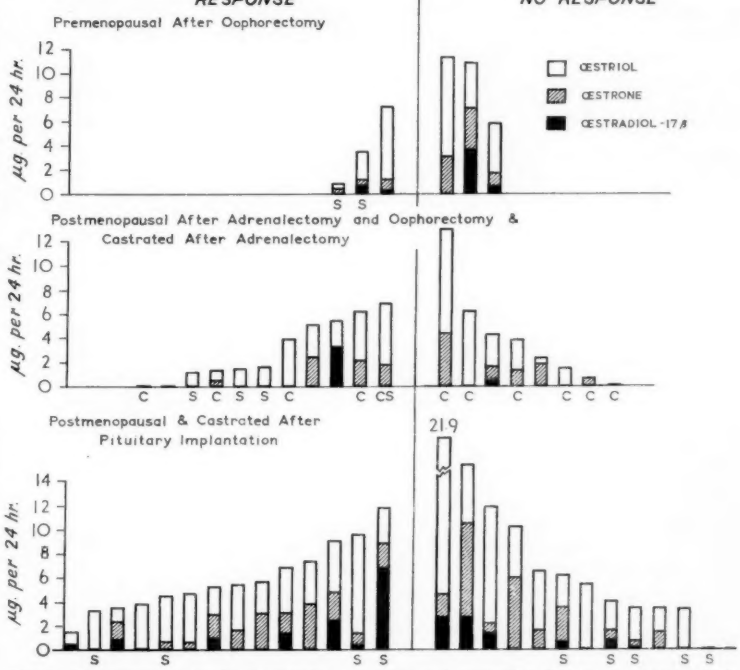

Fig. 2—Postoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of 50 patients with breast cancer treated by endocrine ablation.

S = modified method. C = corticotrophin.

before and after adrenalectomy plus oophorectomy and in fifteen postmenopausal patients before and after pituitary implantation (figs. 3 and 4; tables IX–XII). The clinical response to these operations was not related to change in œstrogen levels. Again it was noted that adrenalectomy plus oophorectomy was followed by a decisive drop in the excretion of the three œstrogens, whereas no consistent change resulted from pituitary implantation.

TABLE V—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY PLUS OOPHORECTOMY AND BY PITUITARY IMPLANTATION

Response of cancer		No.	μg. per 24 hours			
			Œstriol	Œstrone	Œstradiol	Total
Ax	Benefit	11	1·9 ± 0·56	0·8 ± 0·97	0·3 ± 0·29	3·0 ± 0·71
	No benefit	8	2·7 ± 1·13	1·2 ± 0·51	0·1 ± 0·06	4·0 ± 1·48
Hx	Benefit	14	3·5 ± 0·46	1·4 ± 0·30	0·9 ± 0·49	5·8 ± 0·76
	No benefit	13	4·2 ± 1·31	2·2 ± 0·98	0·6 ± 0·96	7·0 ± 1·74

TABLE VI—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN POSTMENOPAUSAL OR CASTRATED WOMEN TREATED BY ADRENALECTOMY

Response of cancer	No. of patients	Mean excretion of œstriol, œstrone, œstradiol	
		μg. per 24 hours	log μg. per 24 hours
Benefit	11	3·0 ± 0·71	0·375 ± 0·104
No benefit	8	4·0 ± 1·48	0·451 ± 0·143
Mean difference		1·0 ± 1·51	0·076 ± 0·19
P		>0·5	>0·6

Discussion

Our results indicate that the preoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of patients with metastatic breast cancer do not influence the response to oophorectomy, adrenalectomy, or pituitary implantation, and that these levels are of no value in predicting the results of endocrine surgery. These findings, although differing from those of Huggins and Dao (1954) with a biological method of assay, are in agreement with those of Birke et al. (1958) who also used Brown's method. The specificity of this method is well established, the results correlating closely with œstrogen estimations carried out simultaneously by bioassay (Bulbrook et al. 1957) counter-current distribution, reverse isotopic dilution (Gallagher et al. 1958), and vaginal smears (Young et al. 1957). Therefore there is little doubt that the lack of relation between the clinical response and the preoperative excretion of œstriol, œstrone, and œstradiol-17β is a reliable finding.

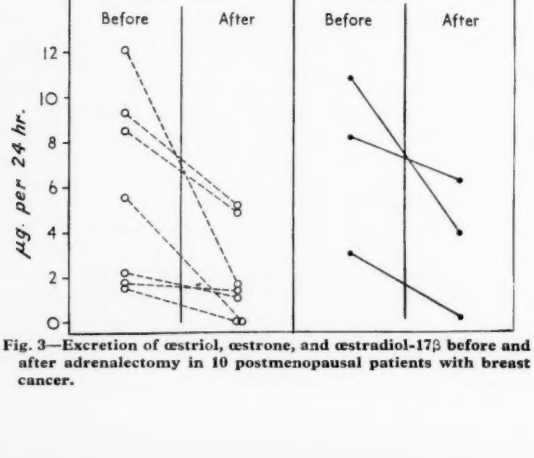

Fig. 3—Excretion of œstriol, œstrone, and œstradiol-17β before and after adrenalectomy in 10 postmenopausal patients with breast cancer.

TABLE VII—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN POSTMENOPAUSAL OR CASTRATED WOMEN TREATED BY PITUITARY IMPLANTATION

Response of cancer	No. of patients	Mean excretion of œstriol, œstrone, œstradiol	
		μg. per 24 hours	log μg. per 24 hours
Benefit	14	5·8 ± 0·76	0·711 ± 0·06
No benefit	13	7·0 ± 1·74	0·703 ± 0·11
Mean difference		1·2 ± 1·85	0·008 ± 0·132
P		>0·5	>0·9

The postoperative estimations are generally less reliable because in many cases they approach the lower limits of sensitivity of the method and were made while the patients were receiving maintenance cortisone, which is known to interfere with the results of Brown's original method (Brown et al. 1957).

In studies reported elsewhere we have been unable to detect significant alteration in the postoperative excretion of œstrogens following stopping of maintenance therapy (Hobkirk et al. 1959) and believe that on the whole the postoperative results reported in this paper do give a valid qualitative estimation of œstrogen excretion.

Adrenalectomy plus oophorectomy regularly resulted in a fall of œstrogen excretion, but neither the extent of this fall nor the postoperative levels were related to the clinical response. Several patients in both responding and non-responding groups continued to excrete significant amounts of the three œstrogen fractions, and in one patient, reported elsewhere, in whom œstrogen estimations were carried out monthly after adrenalectomy plus oophorectomy, levels of up to 10 μg. were regularly found despite a most dramatic clinical remission (Sim et al. 1959).

TABLE VIII—COMPARISON OF EXCRETION OF ŒSTRIOL, ŒSTRONE, AND ŒSTRADIOL-17β AFTER ADRENALECTOMY PLUS OOPHORECTOMY AND AFTER PITUITARY IMPLANTATION

Endocrine surgery	No. of patients	Mean excretion of œstriol, œstrone, œstradiol-17β	
		μg. per 24 hours	log μg. per 24 hours
Adrenalectomy + oophorectomy	19	3·4 ± 0·72	0·407 ± 0·083
Pituitary implantation	27	6·4 ± 0·92	0·707 ± 0·062
Mean difference		3·0 ± 1·25	0·300 ± 0·102
P		<0·02	<0·01

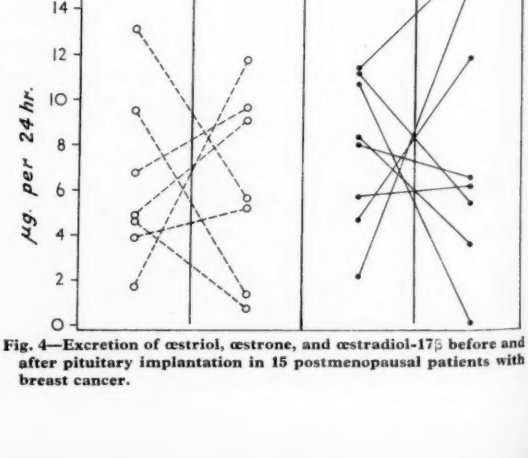

Fig. 4—Excretion of œstriol, œstrone, and œstradiol-17β before and after pituitary implantation in 15 postmenopausal patients with breast cancer.

TABLE IX—MEAN EXCRETION OF ŒSTRIOL, ŒSTRONE, AND ŒSTRADIOL-17β IN 10 PATIENTS BEFORE AND AFTER ADRENALECTOMY PLUS OOPHORECTOMY

Response of cancer	No. of patients	Time of test	μg. per 24 hours			
			Œstriol	Œstrone	Œstradiol-17β	Total
Benefit ..	7	Before	4·3	1·2	0·4	5·9
		After	0·9	0·7	0·5	2·1
No benefit	3	Before	3·8	2·3	1·2	7·3
		After	2·9	0·5	0	3·4

TABLE X—MEAN EXCRETION OF ŒSTRIOL, ŒSTRONE AND ŒSTRADIOL-17β IN 15 PATIENTS BEFORE AND AFTER PITUITARY IMPLANTATION

Response of cancer	No. of patients	Time of test	μg. per 24 hours			
			Œstriol	Œstrone	Œstradiol-17β	Total
Benefit ..	7	Before	4·0	1·8	0·5	6·3
		After	3·2	1·5	1·5	6·2
No benefit	8	Before	6·4	1·2	0·2	7·8
		After	5·3	2·5	1·0	8·8

TABLE XI—MEAN EXCRETION OF ŒSTROGENS IN 10 PATIENTS BEFORE AND AFTER ADRENALECTOMY PLUS OOPHORECTOMY

Time of test	Œstriol, œstrone, œstradiol (μg. per 24 hours)
Before	6·3
After	2·5
Mean difference	3·9 ± 0·98*
P	<0·01

* Standard error of mean difference.

TABLE XII—MEAN EXCRETION OF ŒSTROGENS IN 15 PATIENTS BEFORE AND AFTER PITUITARY IMPLANTATION

Time of test	Œstriol, œstrone, œstradiol (μg. per 24 hours)
Before	7·1
After	7·6
Mean difference	+0·5 ± 1·92
P	>0·7

This finding is in agreement with those of other workers using Brown's method (Strong et al. 1956, Bulbrook and Greenwood 1957, Bulbrook et al. 1958b, Birke et al. 1958) and bioassay (Bulbrook et al. 1958d), although Diczfalusy et al. (1958), using counter-current distribution, were unable to confirm that the Kober chromogens present in the urine of patients after adrenalectomy plus oophorectomy were in fact œstrogens. Possible sources of œstrogens in the urine of patients after adrenalectomy plus oophorectomy have been discussed elsewhere (Hobkirk et al. 1959).

We were unable to show that pituitary implantation had any consistent effect on œstrogen excretion. Those patients who responded to the operation had values similar to those who failed to do so, indicating that the response was unconnected with the excretion of œstrogens. This finding differs from that reported by Bulbrook et al. (1958c) in which those patients who responded to surgical hypophysectomy had lower postoperative values than those patients who failed to benefit.

The adrenal glands are not completely suppressed by removal of the pituitary. Aldosterone secretion is unaffected by total hypophysectomy (McLean et al. 1957) and we have also found that the secretion of androgens and cortisol may continue despite complete destruction of the gland (Forrest et al. 1960). Under similar circumstances œstrogens also may be secreted by the adrenals and ovaries. If this is so, it might suggest that removal of a pituitary factor may be responsible for the remission of breast cancer which may follow destruction of the hypophysis.

Although these studies indicate that the response of breast cancer to endocrine ablation is not related to changes in the excretion of these three œstrogen metabolites in the urine, they do not refute the theory of œstrogen dependence. It must be remembered that œstriol, œstrone, and œstradiol-17β represent only one-quarter of the total œstrogens excreted, and it may be that the active œstrogen is not yet isolated. At the present time evidence for this is lacking, and there appears to be little justification for continuing the practice of referring to breast tumours which respond to endocrine ablation as œstrogen-dependent.

We are indebted to Prof. C. F. W. Illingworth, in whose department of surgery these investigations were carried out, for his interest and criticism. We also wish to thank Miss Shiela E. Tilson, Mr. Neil Carlin, and Mr. Carrick Henderson for technical assistance. This work was supported by the British Empire Cancer Campaign, A. W. Sim, R. Hobkirk, Helen Stewart, and D. W. Blair being in receipt of full-time grants.

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EFFECT OF A SATURATED MEDIUM-CHAIN TRIGLYCERIDE ON SERUM-LIPIDS IN MAN

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BECAUSE natural fats are complex their effects on serum-lipids during feeding experiments in man are very difficult to interpret. The problem might well be clarified by studies using synthetic edible fats of simplified fatty-acid composition.

Malmros (1958) suggested that the rise in serum-cholesterol level observed in man when butter or coconut oil is the sole source of fat may be due to the presence in

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TABLE I—FATTY-ACID COMPOSITION OF M.C.T. BY GAS-LIQUID CHROMATOGRAPHY

A succinate polyester of ethylene glycol was used as the liquid phase, argon as the carrier gas, and strontium 90 was the detector.

Fatty acid	% in M.C.T.
C_8	1·9
C_8	77·7
C_{10}	19·6
C_{12}	0·8

these fats of saturated fatty acids of chain lengths less than C_{16}. Until recently it has been impossible to test this proposition adequately because of technical difficulties and the expense of glycerides containing only shorter-chain fatty acids.

In this study a synthetic fat, medium-chain triglyceride (M.C.T.). was the sole source of dietary fat in formula-feeding experiments on human subjects. The serum-lipid responses obtained with M.C.T. were then compared with those obtained when corn oil or butter was substituted in the formula diet in isocaloric amounts.

Material and Methods

The M.C.T. preparation used in these experiments was extracted from coconut oil. The first fraction, collected by distillation of the fatty acids obtained by hydrolysis from coconut oil, comprises saturated fatty acids of 6–12 carbons. The fatty acids are then reconstituted into triglycerides (Kaunitz et al. 1958). Thus, the C_6–C_{12} fatty acids constitute more than 99% of the fatty acids in M.C.T. The iodine value of M.C.T. is less than 1. At the most only trace quantities of linoleic acid and non-saponifiable sterols are present in the preparation. The melting-point is below 0°C. M.C.T. represents about 15% of the original coconut oil. At room temperature it is a very thin light-yellow clear odourless liquid, with a bland taste.

The fatty acid composition of M.C.T. as determined by gas-liquid chromatography is shown in table I.

Studies were made in the metabolic ward of St. Luke's Hospital on eight patients, one of whom served in two sets of experiments. A formula diet, prepared in a Manton-Gaulin Hospital on eight patients, one of whom served in two sets of dairy-type homogeniser, was the only source of food during the experiments (Ahrens et al. 1954). The formula derived 40% of its caloric content from fat, 17% from protein, and 43% from carbohydrate. Dextrose was the only source of carbohydrate, and a purified casein preparation (' Casec ') was the only source of protein. M.C.T., corn oil (iodine value 130), or butter (80% fat; iodine value 38) was used as a source of fat; each was substituted isocalorically during successive feeding periods without varying the protein or carbohydrate intake. We tried to keep the body-weight of each subject constant by adjustment of formula feeding. Sodium chloride, potassium chloride, and vitamins were given in constant amounts as daily supplements. All blood samples were drawn after an overnight fast. Serum was analysed two or three times per week for total and esterified cholesterol (Sperry and Brand 1943) and lipid phosphorus (Youngberg and Youngberg 1930). All the subjects were given each kind of fat for long enough to achieve a " steady state " with respect to the serum-lipids under measurement. Another fat was substituted isocalorically when three or more successive cholesterol determinations showed that a plateau had been reached. All of the formula diets were well tolerated except during a period of 3–4 days, characterised by nausea and abdominal fullness, before the subjects became adjusted to the M.C.T. formula. But this transient discomfort did not prevent them from consuming and retaining the formula. Moderate constipation was a common complaint regardless of the fat source. No diarrhœa or change in the gross character of the stools was encountered.

TABLE II—SERUM-LIPIDS DURING SUCCESSIVE EXPERIMENTAL FEEDING PERIODS

Mean steady-state data are given, comparing effects of M.C.T. and corn oil in four subjects on formula diets. (Individual peak values are included to indicate the transient early effects of M.C.T.)

Subject no.	Age (yr.)	Sex	Dietary fat	Mg. per 100 ml. serum (steady state)		
				Total cholesterol	Cholesterol ester	Phospholipids
1	42	M	Ad-libitum diet ..	227	169	218
			Corn oil	123	89	128
			M.C.T. (transient peak)	180	132	150
			M.C.T.	139	105	147
			Corn oil	117	89	145
2	46	F	Ad-libitum diet ..	232	169	247
			Corn oil	160	110	187
			M.C.T. (transient peak)	190	140	202
			M.C.T.	171	128	198
			Corn oil	158	105	185
3	54	M	Ad-libitum diet ..	212	164	244
			Corn oil	129	96	207
			M.C.T. (transient peak)	165	121	213
			M.C.T.	144	105	207
			Corn oil	136	100	208
4	52	F	Ad-libitum diet ..	227	167	266
			Corn oil	152	106	205
			M.C.T. (transient peak)	204	152	225
			M.C.T.	150	107	210
Mean ± standard deviation			Ad-libitum diet ..	225 ± 8	167 ± 3	244 ± 20
			Corn oil	141 ± 17	100 ± 10	182 ± 36
			M.C.T. (transient peak)	185 ± 16	136 ± 13	197 ± 32
			M.C.T.	151 ± 14	111 ± 11	188 ± 32
			Corn oil	137 ± 20	98 ± 8	179 ± 32

TABLE III—SERUM-LIPIDS DURING SUCCESSIVE EXPERIMENTAL FEEDING PERIODS

Mean steady-state data only are included, comparing effects of M.C.T. and butter in three subjects on formula diets. The effect of M.C.T. following an ad-libitum diet is shown in two subjects.

Subject no.	Age (yr.)	Sex	Dietary fat	Mg. per 100 ml. serum (steady state)		
				Total cholesterol	Cholesterol ester	Phospholipids
5	62	F	Ad-libitum diet	269	194	275
			Butter	238	175	260
			M.C.T.	177	126	190
			Butter	268	186	258
6	58	F	Ad-libitum diet	259	184	265
			Butter	217	154	226
			M.C.T.	179	131	217
4	52	F	M.C.T.	150	107	210
			Butter	181	134	217
			M.C.T.	131	94	198
7	62	F	Ad-libitum diet	357	258	288
			M.C.T.	275	172	250
8	44	M	Ad-libitum diet	188	140	232
			M.C.T.	168	116	202

Results

Whenever a subject's regime was changed from an ad-libitum hospital diet to a formula diet, serum levels of total and esterified cholesterol, and of phospholipids fell regardless of the type of fat contained in the formula. The degree of fall varied with the nature of the fat in the initial formula (tables II and III). The four subjects who consumed a corn-oil formula after having an ad-libitum diet showed a mean drop in serum-total-cholesterol of 38 ± 6% ‡; the two who were given M.C.T. had a mean drop of 23 and 11%; and the two who had butter showed a mean drop of 16 and 10%.

‡ Standard deviation = $\sqrt{\frac{\Sigma(x - \bar{x})^2}{n-1}}$

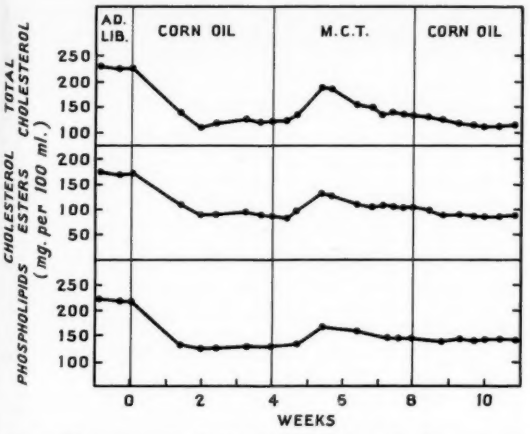

Fig 1—Effects on serum-lipids of a M.C.T. formula diet compared with a formula containing an isocaloric amount of corn oil (subject 1, with a history of " coronary insufficiency ").

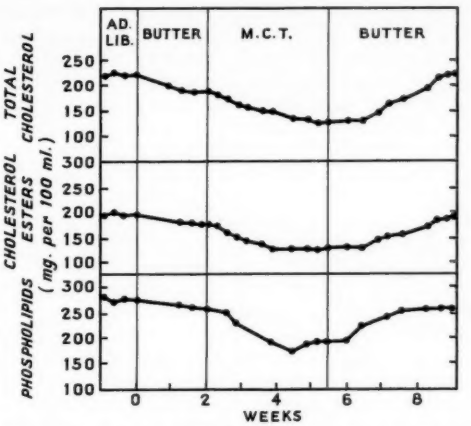

Fig. 2—Effects on serum-lipids of a M.C.T. formula diet compared with a formula containing an isocaloric amount of butter (subject 5, with a history of " coronary insufficiency ").

In the four subjects in whom M.C.T. was compared with corn oil, using each as his own control, the serum-lipids showed a prompt and dramatic drop when the diet was changed from an ad-libitum hospital regime to a corn-oil formula, as was previously reported (Ahrens et al. 1957). When M.C.T. was substituted isocalorically for corn oil, the serum-lipid values rose transiently in every case, with a mean maximal increment of $29\pm15\%$ in 7–10 days (table II). Thereafter the serum-lipids fell gradually over a period of 10–22 days to levels slightly higher than those achieved with corn oil (fig. 1). For example, serum-total-cholesterol levels (steady state) for the M.C.T. periods averaged $8\pm5\%$ higher than the serum-total-cholesterol levels (steady state) during the corn-oil periods, when M.C.T. was given after corn oil. When corn oil followed M.C.T., serum-total-cholesterol levels (steady state) fell by an average of $9\pm6\%$.

In the subjects in whom M.C.T. was compared with butter, the serum-lipid levels increased appreciably when butter followed M.C.T., and decreased appreciably when M.C.T. followed butter (table III and fig. 2). For example, butter induced rises in serum-total-cholesterol of 21 and 51% when it was given after M.C.T., but when M.C.T. followed butter, decreases in the cholesterol level of 27, 26, and 16% were observed.

Discussion

The cholesterol-raising effects of butter and coconut oil have been variously attributed to their low content of linoleic acid (Kinsell and Sinclair 1957), their low iodine value (Ahrens et al. 1957), and their relatively high content of saturated medium-chain fatty acids (Malmros 1958).

Our studies show that the hypercholesteræmic effect of butter in relation to M.C.T. cannot be due to its low content of linoleic acid or to its low iodine value, since M.C.T. contains only a trace of linoleic acid and has an iodine value of less than 1 (butter having an iodine value of about 40). Nor is it likely that the hypercholesteræmic effect of butter is due to its content of medium-chain fatty acids, since M.C.T. by itself has a hypocholesteræmic effect in relation to butter. A possible explanation of the hypercholesteræmic effect of butter might still be that some combination of the fatty acids which it contains has an effect that cannot be predicted from the behaviour of individual fatty acids.

A curious effect of M.C.T. on serum-lipid levels was the transient rise which was produced after 7–10 days. During subsequent weeks the lipid levels fell again to the values attained in the plateau-like phase of the earlier period. This emphasises the difficulties of interpreting the results of formula-feeding experiments over periods of the order of 10 days or less.

Ahrens et al. (1957) have rated fats in terms of their effect on serum-total-cholesterol in relation to the effect of corn oil used as a standard. According to this classification, M.C.T. seems to fall into the same category as olive oil, and this observation is difficult to reconcile with the hypothesis of Ahrens et al. that the hypercholesteræmic effect of a fat in relation to corn oil is best explained as a function of iodine value. The results of our studies are more consistent with the suggestion that the effect of a dietary fat on serum-cholesterol can be related to certain of its physical characteristics. By shortening the chain length of its constituent fatty acids, a fully saturated triglyceride acquires such properties as a low melting-point and greater miscibility with water—properties usually associated with a high degree of unsaturation (Deuel 1951).

Rittenberg et al. (1937), Longenecker and Hilditch (1938), and Longenecker (1939) have shown that the saturated fatty acids with less than 12 carbon atoms, when ingested, are not significantly stored in animal depot fats. More recently Geyer et al. (1951) have shown that a shorter-chain fatty acid, such as octanoate, serves as an active substrate for oxidation but is not readily used for synthesis. On the other hand a longer-chain fatty acid, such as palmitate, may serve equally well as a substrate for oxidation or synthesis depending on the metabolic circumstances. But our studies do not show whether this dissimilarity in metabolism of fatty acids of differing chain lengths can account for the effect on serum-lipid levels of a highly saturated fat like M.C.T.

Since corn oil is one of the most effective oils in lowering serum-cholesterol levels, it is noteworthy that M.C.T., a triglyceride with properties strikingly different from those of corn oil, raised the cholesterol levels in this small series in relation to corn oil by less than 10%. Corn

oil and M.C.T. are at opposite ends of the lipid spectrum so far as iodine value, linoleic-acid content, and chain length are concerned. The only characteristics they have in common are their liquid character at room temperature, relatively greater miscibility in water, and solubility in organic solvents.

Summary

A medium-chain triglyceride preparation (M.C.T.), containing saturated fatty acids with chain lengths ranging from C_6 to C_{12}, was incorporated into a formula-type diet and given as the sole source of fat to eight human subjects. The effect on serum-lipids was compared with that of formula diets containing isocaloric amounts of corn oil and butter.

Compared with corn oil, M.C.T. induced a slight rise in serum-total-cholesterol when the experimental periods were long enough to permit a "steady state". In the subjects in whom M.C.T. was compared with butter, the serum-lipids increased appreciably when butter followed M.C.T., and decreased appreciably when M.C.T. followed butter.

Thus the cholesterol-raising effect of butter cannot be due wholly to its content of medium-chain fatty acids, since M.C.T. given alone lowers cholesterol levels in relation to butter. The hypercholesteræmic effect of butter is difficult to explain in terms of iodine value, since the iodine value of M.C.T. is much less than that of butter. The cholesterol-lowering effect of M.C.T. cannot be explained in terms of the content of linoleic acid or other polyunsaturated fatty acids, since they are not present in this preparation.

Characteristics shared by M.C.T. and the cholesterol-lowering oils, such as corn oil, are a low melting-point, relatively high miscibility in water, and increased solubility in organic solvents. Possibly metabolic differences between M.C.T. and triglycerides containing longer chain fatty acids might influence their effects on serum-lipids.

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Addendum

Since this article was submitted, we have become aware of a study of the effect of dietary cholesterol on plasma-cholesterol levels (Beveridge, J. H. R., Connell, W. F., Haust, H. L., Mayer, G. A. *Canad. J. Biochem. Physiol.* 1959, **37,** 575) in which a feeding experiment utilising M.C.T. was described. A formula-type diet providing 30% of its calories from M.C.T. was fed for 8 days to a group of subjects previously on an isocaloric fat-free formula regime. During this short experimental period the serum-total-cholesterol did not change significantly.

HUMAN FŒTAL THYROGLOBULIN

WITH PARTICULAR REFERENCE TO THE ÆTIOLOGY OF HASHIMOTO'S DISEASE

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ANTIBODIES to thyroglobulin have been found in the serum in various disorders of the thyroid gland, particularly Hashimoto's disease (Roitt and Doniach 1957). Experimental work by Witebsky (1957) suggests that this disease, at least, is caused by the action on the thyroid of antibodies produced by the patient's own tissues. As antigens introduced into the body during fœtal development generally induce immunological tolerance instead of an antibody response (Billingham et al. 1956) we thought it might be of interest to determine the age at which the fœtal thyroid gland begins to contain thyroglobulin.

Investigation

Materials and Methods

Fœtal thyroid glands.—Sixteen fresh fœtuses weighing 20 g. to 3000 g. were used. The thyroid glands were dissected out, weighed, and homogenised in 1–2 ml. of physiological saline solution. In most cases a small fragment of the gland was examined histologically after fixation in formalin.

Antiserum was produced in rabbits by immunisation with highly purified adult thyroglobulin, prepared as described previously (Korngold, van Leeuwen, and Brener 1959). It could detect the homologous antigen in quantities of less than 0·5 mg. per ml. Immunological analyses were done by the Ouchterlony technique as described by Korngold et. al. (1959).

Results

Since the immunological test used is not very sensitive, only the positive findings are significant. The table

RELATION BETWEEN FŒTAL MATURITY AND PRESENCE OF THYROGLOBULIN

No. of specimen	Weight of fœtus (g.)	Crown-rump length of fœtus (cm.)	Approx. age in weeks (Potter 1952)	Weight of thyroid (mg.)	Presence of thyro-globulin
1	3000	..	40	1090	+
2	3000	..	40	..	+
3	1600	28·0	32	750	+
4	1200	30·0	32	..	+
5	1110	..	30	250	+
6	920	25·0	28	400	+
7	880	..	26	450	+
8	780	22·0	26	270	+
9	770	21·0	26	210	+
10	460	18·8	23	200	+
11	420	20·0	23	150	+
12	278	12·5	18	100	−
13	127	13·8	18	50	−
14	115	12·0	16	35	−
15	39	9·5	14	30	−
16	20	7·2	12	..	−

shows that a substance antigenically indistinguishable from thyroglobulin was present in fœtuses the youngest of which was about 23 weeks old (no. 11). The precipitation lines formed by the fœtal thyroid extracts fused completely with the line of the adult thyroglobulin, indicating that fœtal thyroglobulin is immunologically identical with the adult form.

Histological examination showed thyroid acini in all the glands examined (nos. 1–4, 6, 7, 9, 11, 14). In most cases some of the vesicles contained colloid. There was, however, no good correlation between the age of the

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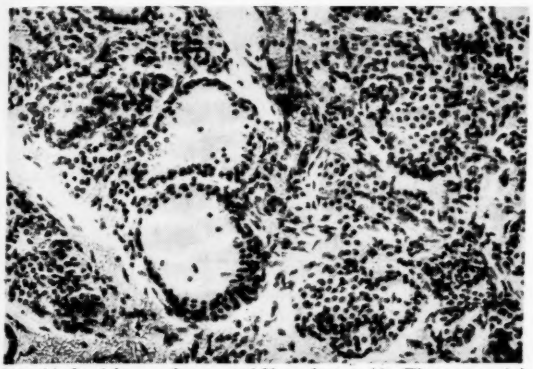

Thyroid gland from a fœtus aged 23 weeks (no. 11). There are acini in various stages of development, some of which contain colloid. (Hæmatoxylin and eosin. × 200.)

fœtus and the proportion of colloid-containing acini. This is in agreement with the work of Lelkes (1933). The figure shows the histological appearance of the thyroid gland in the youngest fœtus in which thyroglobulin was found.

Discussion

Radioactive iodine studies (Hodges et al. 1955, Chapman et al. 1949) have shown that the fœtal thyroid gland begins accumulating ^{131}I at the age of about 14 weeks. This function is acquired simultaneously with the appearance of colloid in some of the acini. Our investigation confirms that the human thyroid gland has begun to function by the 23rd week (4 months before birth). If our assay methods had been more sensitive we might have found that the appearance of thyroglobulin, like the accumulation of ^{131}I, coincides with the development of colloid in the thyroid gland at about 14 weeks gestation (about 6 months before birth).

There are two mechanisms by which body components may become antigenic. They may not yet be developed when tolerance to the body's own proteins is established, or they may normally have no opportunity to make contact with the body's mesenchymal cells (Burnet 1959). The critical age, after which tolerance is no longer present, varies in different species and even with different antigens (Billingham et al. 1956). Nevertheless, man is not likely to be an exception to the rule that tolerance ceases at about the time of birth. Our finding of thyroglobulin in fœtal thyroid glands 4 months before birth supports the view that thyroglobulin can act as an autoantigen, because normally the antigen is confined to the thyroid acini and does not reach the reticuloendothelial system.

In Hashimoto's disease thyroglobulin has been observed outside the thyroid follicles (White 1957). This may be related to an abnormality of the basement membrane (Stuart and Allan 1958). Once thyroglobulin has escaped from the acini an immune response occurs which may cause further damage and thus perpetuate a vicious circle. The origin of the initial injury which allows leakage of thyroglobulin from the acini, is, however, still unknown.

Summary

A substance antigenically indistinguishable from thyroglobulin was found in fœtal thyroid glands. The youngest of these fœtuses was about 23 weeks old. The gland showed colloid-containing acini.

These results are keeping with the view that thyroglobulin is potentially autoantigenic because it is normally confined to the thyroid acini and does not come in contact with the body's antibody-forming mechanism.

The bearing of these findings on the ætiology of Hashimoto's disease is discussed.

We are grateful to Prof. C. Tupper and Prof. R. L. de C. H. Saunders of the departments of obstetrics and anatomy, Dalhousie University, for permission to study the fœtuses.

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Preliminary Communications

CHANGES IN RENAL AND URINARY ALKALINE PHOSPHATASE CONTENT FOLLOWING X-IRRADIATION OF THE RAT KIDNEY

X-IRRADIATION of the kidneys in the rat is followed by hypertension after a mean latent interval of 230 days.[1] The blood-pressure was found to rise before the development of diffuse structural changes commonly described as "irradiation nephritis" or "sclerosis". It seemed possible that histochemical studies might reveal changes in enzyme content of the kidney in relation to the onset of hypertension. Studies of alkaline phosphatase showed a marked reduction in this enzyme soon after irradiation, with a return to normal long before hypertension developed.

INVESTIGATION

Twelve normotensive female rats of the Wistar strain, aged between 80–90 days and weighing 150–200 g., were exposed to 1200r irradiation of the kidneys by the technique of Wilson et al.[1] They were killed serially at 1, 3, 5, 10, 20, and 40 days after irradiation. The kidneys were immediately fixed in 80% ethyl alcohol, embedded in paraffin, and sectioned at 5 μ. Alkaline phosphatase was demonstrated by the cobalt-sulphide technique of Gomori[2]; sodium-β-glycerophosphate was used as substrate for an incubation period of 2 hours. Three control animals received 1200r to the chest wall.

Urinary alkaline phosphatase was studied in another series of twelve animals of similar age and weight. Measurements were made for a baseline period of 7 days; thereafter six animals received 1200r irradiation to the kidneys while the remaining six served as controls. Urinary phosphatase was estimated for 10 consecutive days after irradiation. Measurements were made by the technique of Scott and Huggins,[3] the system being buffered at pH 9·2. A fivefold dilution of urine had to be used since it was found that with undiluted urine the ultimate colouration was too intense for estimation to fall within the most sensitive range of the photoelectric colorimeter, using a 6600 Å filter. Serum alkaline phosphatase was also estimated on the 2nd and 6th day of the baseline period and the 3rd and 7th day of the post-irradiation period by the King and Armstrong[4] technique.

Non-irradiated animals showed alkaline phosphatase in the brushborders, nuclear membranes, nucleoli, and

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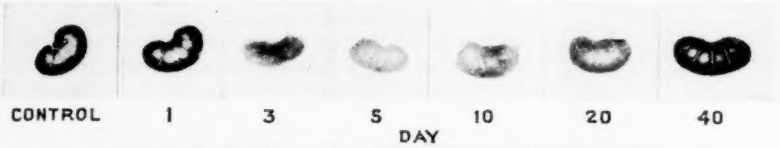

Fig. 1—Alkaline phosphatase in rat kidney after 1200r band irradiation.

mitochondria of the proximal convoluted tubule cells. A day after irradiation mitochondrial positivity was lost but the other sites of enzymic activity were not affected until 3 days after irradiation. A striking diminution in positivity of the brushborders occurred at this time and persisted until 40 days after irradiation, when full activity was restored and the kidneys were once more indistinguishable from those of non-irradiated control animals (fig. 1). No change in renal alkaline phosphatase was demonstrated in the three animals which received irradiation to the chest wall.

Urinary alkaline phosphatase content was inversely related to renal alkaline phosphatase positivity. Maximal urinary concentration occurred between the 3rd and 8th day after irradiation (fig. 2). There was no change in serum alkaline phosphatase concentration after irradiation. Casts were absent from the urine and urinary pH was not altered by irradiation.

COMMENT

Breedis et al.[5] demonstrated that, when nephrosis was induced in rats with uranium nitrate, loss of renal alkaline phosphatase was associated with increased urinary excretion of the enzyme. They found 15–46% of the total urinary phosphatase activity in the low-speed sediment in casts and other particulate matter; the remainder was thought to be incorporated in finely divided or soluble debris of the tubular cells. Pasqualino and Bourne [6] observed loss of renal alkaline phosphatase up to the 8th day after renal artery clipping in rats. Spink and Landeryou [7] noted loss of renal alkaline phosphatase in a variety of mammals, including man, as a result of endotoxin shock. The varied nature of the insults which decrease renal alkaline phosphatase suggests that such loss represents a non-specific response to injury. The observed increase in urinary excretion of the enzyme could not be related to the presence of casts, nor is it likely to be due to increased renal clearance, since serum levels showed no significant change following irradiation. It appears therefore that " leakage " of alkaline phosphatase from the brushborders of the proximal convoluted tubule cells into the urine is the most likely explanation. Estimation of renal and urinary alkaline phosphatase might therefore be useful as an index of tubular damage due to irradiation and other forms of renal injury. So far, however, these studies have not shed further light on the mechanism of the hypertension which follows irradiation of the kidneys.

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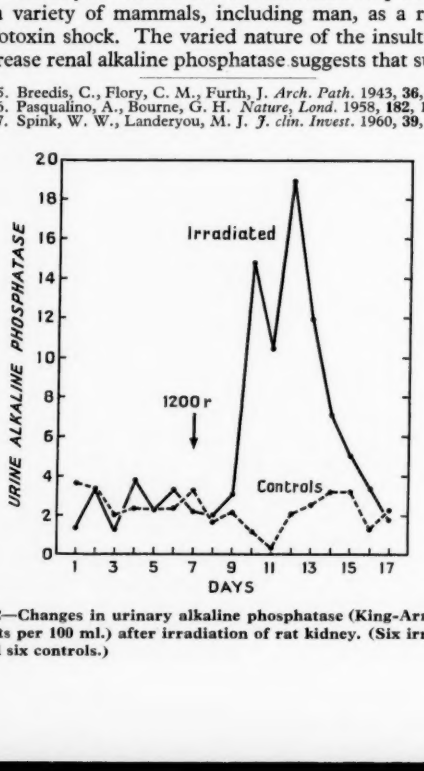

Fig. 2—Changes in urinary alkaline phosphatase (King-Armstrong units per 100 ml.) after irradiation of rat kidney. (Six irradiated and six controls.)

We are grateful to Prof. Clifford Wilson and Dr. J. M. Ledingham for their advice.

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NEW ANTIVIRAL CHEMOTHERAPEUTIC AGENT ACTIVE AGAINST SMALLPOX INFECTION

ALTHOUGH smallpox vaccine has been used for over a hundred and sixty years the disease is still prevalent in many parts of the world, and in 1956 from those countries for which records are available 60,431 cases were reported with 31,622 deaths (52·2%),[1] and the actual number of cases must have been much higher. In Burma, where vaccination is compulsory, there were 4223 notified cases with 1495 deaths (35·4%). There is therefore a definite need for a specific antiviral chemotherapeutic agent in the treatment of the disease.

Isatin β-thiosemicarbazone has a pronounced chemotherapeutic effect in mice infected intracerebrally with neurovaccinia virus, and will protect against death after the injection of doses of virus up to 100,000 L.D.$_{50}$.[2] It has no apparent effect in mice infected intracerebrally with ectromelia virus,[3] but it has a clear chemotherapeutic effect in mice infected with rabbitpox.[4] A considerable number of derivatives of isatin β-thiosemicarbazone have been prepared and tested for antiviral activity,[5] and some have been found to be considerably more active than the parent compound. In view of the activity of compounds of this type against two representatives of the pox virus group it was of interest to see whether they would also have an effect in infections with smallpox virus. N-ethylisatin β-thiosemicarbazone, which was the derivative with the greatest activity against neurovaccinia virus, was chosen for this purpose.

MATERIALS AND METHODS

The work was carried out with the Schofield strain of alastrim virus. This was received as the seventh passage on the chorioallantoic membrane, and after one further passage on the membrane it was carried through three intracerebral passages in infant mice. The virus produces a fatal infection in mice up to 6 days of age; in older mice signs of encephalitis

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THERAPEUTIC EFFECT OF N-ETHYLISATIN β-THIOSEMICARBAZONE IN MICE INFECTED WITH ALASTRIM VIRUS

Expt no.	Treated				Controls		
	Dose level (mg. per kg.)	No. of mice	Died	Remained well	No. of mice	Died	Developed encephalitis and recovered
1	250·00	9	0	9	8	7	0
2	25·00	9	0	9	9	9	0
3	10·00	9	0	9	8	5	3
4	10·00	7	0	7	6	6	0
5	5·00	6	1	5	6	6	0
6	5·00	9	3	6	9	6	0
7	5·00	11	0	11	12	8	0
8	2·50	11	0	11		As expt 7	
9	2·50	8	1	7	8	3	5
10	1·25	11	1	10		As expt 7	
11	1·00	6	0	6	6	5	1
12	0·50	6	0	6		As expt 11	
13	0·50	8	1	7	8	5	3
14	0·25	8	3	5		As expt 13	
Totals	..	118	10	108	80	60	12

Dose conferring 50% protection ≤0·25 mg. per kg.

develop but many of the animals recover, and mice weighing 10 g. or more show no signs of illness.

The tests of chemotherapeutic activity were carried out in litters of mice of the same age and not more than 6 days old. The litters were pooled and redistributed to the mothers at random. The mice were then infected intracerebrally with a dose of virus containing about 10^2 mouse L.D.$_{50}$ or 10^4 pock-forming units. N-ethylisatin β-thiosemicarbazone was made up as a suspension in distilled water. The mice were weighed, and the dose selected for the experiment was injected subcutaneously with a micrometer syringe in a volume of 0·01–0·03 ml. The compound was injected at the time of infection or up to six hours later. In experiments with dose levels less than 25 mg. per kg. body-weight the dose was repeated once each day for five days.

RESULTS

The results of a number of separate experiments are shown in the accompanying table. After four to five days the control mice showed signs of cerebral irritation, with occasional convulsions, followed by flaccid paralysis of one or more limbs, loss of weight, and death after five to ten days. In the first experiments high doses (25 and 250 mg. per kg.) of N-ethylisatin β-thiosemicarbazone were given in order to establish whether the compound had any antiviral effect. The treated mice showed no signs of illness at any time and were discarded in apparent health after four weeks. Further experiments were then carried out with dose levels down to 0·25 mg. per kg., also with positive results. Thus, of 80 untreated mice 60 died and 12 developed encephalitis and recovered; whereas of 118 mice treated with N-ethylisatin β-thiosemicarbazone in dose levels ranging from 0·25 to 250 mg. per kg. 10 died and the remaining 108 survived without showing any signs of illness. The dose level which conferred 50% protection against infection was around 0·25 mg. per kg. The compound is of low toxicity; mice will tolerate a subcutaneous injection of 500 mg. per kg. given over a period of five days without showing signs of illness, and the therapeutic index is therefore greater than 2000.

CONCLUSIONS

The experiments thus demonstrate that N-ethylisatin β-thiosemicarbazone will protect mice against death and development of apparent illness after intracerebral infection with up to 10^2 L.D.$_{50}$ of alastrim virus, and that protection can be obtained with a dose level as low as 0·25 mg. per kg. An activity of this order is greater than that of the sulphonamides or the tetracyclines against bacteria, and gives reason to expect that N-ethylisatin β-thiosemicarbazone will be of clinical value in treating smallpox in man.

SUMMARY

Infant mice infected intracerebrally with 100 L.D.$_{50}$ of alastrim virus could be protected against death and the development of encephalitis by treatment with N-ethylisatin β-thiosemicarbazone at a dose level of 5 mg. per kg. The compound has a low toxicity and the therapeutic index is greater than 2000. The antiviral chemotherapeutic activity found in animal experiments is thus high enough to suggest that N-ethylisatin β-thiosemicarbazone may be of value in the specific treatment of smallpox in man.

We are grateful to Prof. A. W. Downie and Dr. K. R. Dumbell for providing the strain of alastrim virus and for much useful advice.

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Medical Societies

BRITISH ORTHOPÆDIC ASSOCIATION

THE spring meeting of the British Orthopædic Association was held in Glasgow, in conjunction with the Dutch Orthopædic Society and the Hand Clubs of Great Britain, on April 7–9. The president, Mr. H. J. SEDDON, was in the chair. We publish below a summary of a few of the contributions.

Hand Surgery

Mr. I. A. MCGREGOR (Glasgow) described the different methods of skin grafting in the hand. He divided the grafts into free grafts and flaps. Free grafts could be whole thickness or split. Each had their advantages and disadvantages. The thinner the graft the more likely it was to take, but a thin graft tended to develop a contracture so that it often needed to be replaced later. In traumatic lesions early skin cover was essential to reduce fibrosis to a minimum. The graft must be applied to a suitable bed free from dead tissue and capable of capillary formation. Bone, cartilage, or tendon were unsuitable. The free graft should overlap the defect and be fixed in position with sutures, the excess graft being removed at the first dressing. A bed unsuitable for a free graft was filled by a flap. A large defect might require an abdominal flap, intermediate defects a cross-forearm flap, and a smaller defect a cross-finger or thenar flap.

Mr. M. N. TEMPEST (Chepstow) said that the early differentiation between dead and living tissues in fresh soft-tissue injury was very important. Viability could be determined by the intravenous injection of either disulphine blue or kiton-fast green, which stained all living soft tissue whereas avascular tissues remained unchanged. Maximum staining was reached in 3–5 minutes and the dye was excreted by the kidney in about 48 hours. But Mr. G. BONNEY (London) wondered whether such early differentiation of avascular tissue would not result in tissue being excised which, given time, might have recovered; and Mr. Tempest agreed that this might apply to some tissues rendered temporarily avascular by tension.

Mr. C. C. JEFFERY (Exeter) said that open reduction and fixation of fractures of the hand was not often necessary but was of great value in certain cases: (1) displaced transverse and comminuted fractures in which closed methods had failed; (2) when external fixation would not maintain the position; (3) displaced or angulated fractures arriving late for treatment; (4) if vascular embarrassment rendered external splintage inadvisable; (5) when there was loss of bone. Kirschner wires provided a good form of internal fixation and a dental drill was

useful in inserting them. The wire should not traverse a joint which was intended to function again. Certain oblique fractures including those into interphalangeal joints were fixed with transfixion pins. Bone loss could be made good with cancellous bone from the ilium.

Discussing motor and sensory recovery following repair of median and ulnar nerve lesions at the wrist, Mr. DONAL BROOKS (London) said that motor recovery must take precedence over sensibility; so tendons and bones must be repaired first, though clearly the sooner nerves were repaired if they alone were damaged the better. After repair of distal lesions of the ulnar nerve good motor recovery occurred in 4 out of 5, and of the median nerve in 2 out of 3. On the sensory side, 4 out of 5 repairs of both nerves gave useful recovery and 2 out of 3 reached the grade in which there was no over-reaction. When one digital nerve was divided overlap from the other would take care of the anæsthetic area, but when both were divided they must be repaired. He said that the right time to do nerve repair was when local conditions were most favourable, and there was no logical reason for primary repair. Normal sensibility could never be restored after nerve repair; so the first consideration must be the recovery of protective sensibility. If there was more recovery, so much the better; but the value of the recovery of sensibility depended on the use the patient made of it.

Mr. P. S. LONDON (Birmingham) said that such great advances had been made in the reconstruction of the mutilated hand that it was too often assumed that these extensive procedures were always necessary. It should be remembered that there were many failures, but these were not usually recorded. He advocated a simple approach: the minimum requirements of a useful hand were normal or near-normal sensitivity and two digits that could be brought together firmly and separated. Tactile gnosis as defined by Moberg was not to be expected in any graft which had been separated from its normal nerve-supply, though many would attain protective sensitivity. The initial operation was all important. Often all that was necessary was wound toilet with preservation of as much normally sensitive skin as possible. Small remnants of digits with normal skin should be preserved, but digits which had been denuded were usually better amputated. The object of treatment should always be the earliest possible return to function of a hand unencumbered by stiff or insensitive fingers. If this simple approach was followed many hands would be ready for use after only one operation, and within a few weeks, which had great psychological advantages.

Prof. J. I. P. JAMES (Edinburgh) said that most patients were first seen by casualty officers, however much we would like it to be otherwise. Casualty officers should be taught the essentials of treatment: wound excision, hæmostasis, skin cover, bandage with compression in a good position and elevation. If this were done the hand would be in good condition for subsequent reconstruction if necessary. Mr. MUIR disagreed: he thought that patients with severe injuries of the hand should be transferred to special centres where expert treatment was available. In modern times distance was no bar. Immediate reconstruction was advisable and initial skin dressings should be given up.

Mr. NORMAN CAPENER (Exeter) supported the idea of simplicity in treatment; unnecessary details should be eliminated. Good early treatment was essential, and the mutilated hand was as much of an acute emergency as anything in general surgery.

Avascular Necrosis and the Head of the Femur

Mr. JAMES PATRICK (Glasgow) said that the changes involved in avascular necrosis were different in cortical and cancellous bone, and in a fracture of the neck of the femur it was cancellous bone that was involved. Firstly, there was a relative increase of density which was not always due to ischæmia, but even in the presence of ischæmia union would occur. Secondly, there was a great increase in density due to mechanical collapse. Normal fresh cancellous bone would not collapse if hammered, but if it had been kept at body-temperature for a year it would readily do so. Thirdly, a pathological fracture occurred in the upper part of the femoral head. Immediately after a subcapital fracture viability of the head was in doubt. He advocated the use of a graft and a nail to improve the vascularity of the head and provide fixation. The graft should never be introduced as far into the head as the nail because if the neck collapsed the graft, which would have united to the trochanter but not to the avascular head, would protrude into the joint. If, when the nail was introduced, blood emerged from the central hole, the head was viable. If blood could reach the bone cells in the femoral head within 15 days it would survive. For this reason operation should be as early as possible. If avascular necrosis needed treatment he advised in elderly people an Austin Moore prosthesis and in younger patients a trochanter-to-acetabulum arthrodesis. The high incidence (70%) of avascular changes in children as compared with adults (50%), and in old age (10%), must indicate that blood-vessels cross the epiphysial line.

Perthes' Disease

Dr. J. E. ENKLAAR (Amsterdam) said that in the course of treating a child's hip in which Perthes' disease had been unresponsive to the usual conservative measures he had explored the joint. In the course of the operation he had ruptured the ligamentum teres which did not bleed. It was left in the joint. Subsequent reconstitution of the femoral head had been surprisingly rapid. Since then he had explored similar hips and had found the ligamentum teres to be shortened and unusually inelastic, so that when put on the stretch it produced deformity of the femoral head. Examination of controls showed that the normal ligamentum teres contained thick-walled arteries and many arteriovenous shunts regardless of age. There was a regular pattern of fine elastic fibres lying in parallel lines and a meshwork of autonomic nerve fibres. The ligamentum teres removed from 10 patients with Perthes' disease showed consistently a second pattern of coarse fibres running at an angle to normal ones, and there was fragmentation of the autonomic nerve-fibres but no vascular abnormality. He believed that changes in the autonomic nerve mechanism during growth resulted in the abnormal inelasticity of the ligament. Unless this shortened ligament was either divided or relaxed in flexion (as he had done more recently) the changes in the capital epiphysis would persist.

Congenital Dislocation of the Hip

Mr. J. A. WILKINSON and Dr. C. O. CARTER (London) had investigated 200 children with congenital dislocation of the hip treated conservatively. Results were seldom good in bilateral dislocations but could be successful when the condition was unilateral. The outcome of treatment of unilateral dislocations could be foretold by an examination of the opposite hip. If, after making allowance for age and sex, the roof of the opposite acetabulum was unduly oblique the result of treatment was likely to be unsatisfactory. 149 patients were followed-up. All but 8 had started treatment within the first 3 years of life and had been followed for 5–10 years. There were 17 boys and 132 girls; 107 unilateral and 42 bilateral dislocations. The results of bilateral dislocations were unsatisfactory and those unilateral dislocations in which the opposite acetabulum had a sloping roof were equally poor.

A fairly accurate prognosis was thus possible at the child's first attendance. The minority in whom the outlook was poor and those with bilateral dislocations might be better treated by surgery.

Mr. E. W. SOMERVILLE (Oxford) said that in those hips with only minor displacement it was wrong to say that the acetabular roof was shelving. This was only the radiological appearance due to the delay of ossification, which was always seen in the presence of instability. The acetabular roof was in fact normal in shape but cartilaginous. Treatment by operation had been equally successful in unilateral and bilateral dislocations.

Transplants of Bone

Dr. M. S. KINGMA (Amsterdam) said that Dutch orthopædic surgeons had gained great experience in the use of heterogenous bone by the use of refrigerated calf bone supplied by the bone

transplantation service of the Netherlands Red Cross. At first the results were encouraging. Most wounds healed by first intention but sinuses developed in a few. But later too many fractures showed persistent non-union. He said that transplantation of calf bone would succeed only under the most favourable conditions. The patient must be young; there must be good contact, firm fixation, and prolonged immobilisation. In fact, calf bone was only useful in children for filling bone cavities. Experience with homogenous bone showed that it was useful as a graft but less good than autogenous bone. It was useful if autogenous bone was not available or in insufficient quantity. It should not be used in spondylolisthesis in adults, for extra-articular arthrodesis, or for bridging defects.

Mr. JOHN CHALMERS (Edinburgh) said that there was a widespread belief that the more immature a tissue the more likely it was to survive when transplanted as a homograft. He had carried out experiments with a strain of mice which by inbreeding had achieved such purity that homografts could be exchanged between individuals as readily as autografts. These were called isografts. Femurs from 18-day fœtal mice were implanted both as isografts and homografts into the spleens of adult mice. At this age the femurs were mainly cartilaginous with a small ossific nucleus. Each continued to grow equally up to the sixth day. After that the cartilage of the isograft grew and was progressively replaced by bone, the secondary centres of ossification developing at the right time.

In the homograft the cartilaginous part continued to grow but bone replacement ceased and the bone underwent necrosis. These findings were strictly in accordance with the findings of transplanted adult homografts of bone and cartilage and showed that immature homografts had no advantage over mature homografts.

Reviews of Books

Osteochondritis Dissecans

I. S. SMILLIE, CH.M., F.R.C.S.E., F.R.F.P.S., lecturer in charge, department of orthopædic surgery, University of St. Andrews. Edinburgh: E. & S. Livingstone. 1960. Pp. 224. 60*s*.

Ambrose Paré was once called to see a master-tailor, living in the Rue Saint Honoré, who had a painful swollen knee. He incised the joint, and out fell a loose body. That was four centuries ago, and the first recorded instance of an arthrotomy: yet it is interesting to reflect that very few operations have changed as little as this one, and, until very recently, any contemporary orthopædic surgeon would have managed the case in essentially the same way. Unfortunately such treatment leaves a great deal to be desired when the fragment is derived from an articular surface, and there remains at its site of origin a gross irregularity which will provoke a secondary degenerative arthritis.

In this monograph, Mr. Smillie reviews four distinct conditions, occurring in different age-groups, which give rise to loose bodies, and have in common a radiological picture usually described as that of "osteochondritis dissecans". He goes on to show that if a loose body be replaced in its bed (after this has been freshened with a gouge or drill) it will heal back in position, and he has developed special instruments to facilitate this task of reposing and retaining the fragment.

This is a valuable advance in the treatment of a disease which once carried a gloomy prognosis for the function of the joint. Mr. Smillie's methods have already been widely tried and acclaimed, and his colleagues will find this book an attractive guide to the minutiæ and rationale.

A Textbook of Human Embryology

R. G. HARRISON, D.M., Derby professor of anatomy, University of Liverpool. Oxford: Blackwell Scientific Publications. 1959. Pp. 244. 45*s*.

Professor Harrison's book includes the findings of recent investigations not yet mentioned in other textbooks of human embryology. With many of these, especially in connection with endocrinology, spermatogenesis, and patterns of vascularisation in organs, the author himself has been concerned. He has much reduced and simplified the later development of organs and systems; and in contrast he has emphasised what are sometimes called more "fundamental" matters. Histogenesis of nervous tissue occupies no less than 9 pages (in a relatively small book), whereas development of the entire brain is covered in a mere 13 pages. With this and similar changes of emphasis many readers will be in accord.

A more succinct account of cardiac development is welcome, but the same brevity might usefully have been applied to the urogenital system. Figures of the vascular tree of the testis are almost as numerous as those illustrating the entire development of the heart or brain. These figures are excellent photographs of the author's preparations, contributing to the generally high standard of the volume's illustration.

In treating brain development the author assumes that the reader will be familiar with the details of final form, which he rightly omits. Nevertheless, much space is devoted to purely topographical description of the reproductive organs; and even the inguinal canal receives about $^1/_2$ page of text and 3 large illustrations (2% of the volume's 144 figures). These accounts do not depart from the information usually acquired in the dissecting-room.

Despite what may seem to some readers to be occasional lack of proportion, Professor Harrison's text is a courageous departure. Particularly to be applauded is his realisation that much minute detail can be jettisoned without loss of understanding. Obviously he favours the growing conviction that attention to the basic processes of ontogeny greatly illuminates the particulars and makes them more interesting.

Leukocyte Antigens and Antibodies

ROY L. WALFORD, M.D., assistant professor of pathology, University of California School of Medicine, Los Angeles. New York and London: Grune & Stratton. 1960. Pp. 182. $6.75.

THIS monograph is the first in English on the subject. Much work on leucocyte antigens has been published, as the bibliography of 567 references shows, but there is confusion and contradiction. Dr. Walford's critical survey is especially valuable in the important chapter on technique, in which he clearly indicates which methods he thinks will give the best and most consistent results. Much of the book is devoted to a technical discussion of immunohæmatology. It is clear that most leucoagglutinins are produced by blood-transfusion and are therefore isoantibodies. Antibodies apart from transfusion-produced ones are rare and may be autoantibodies. The recorded incidence of these leucocyte autoantibodies is reviewed, but the results are still far from clear and even the mechanism of drug-induced leucopenia has not been elucidated. Dr. Walford also discusses the relation of the L.E.-factor phenomenon to leucocyte antibodies, and the importance of leucocyte antibodies in the homograft reaction. The chapter on clinical significance shows that the application of tests for leucocyte agglutination is at present limited, but they are becoming part of the investigation of leucopenic states. Anyone beginning work on this subject will find this monograph a most valuable summary and a useful guide to what is known.

Data for Biochemical Research

Editors: R. M. C. DAWSON, D. C. ELLIOT, W. H. ELLIOTT, K. M. JONES. London: Oxford University Press. 1959. Pp. 299. 63*s*.

THE laboratory worker is well used to handbooks such as the "Rubber Book" of the chemist, and he has received with gratitude the data brought together in the Merck and Geigy manuals. This volume is a very welcome addition to the new species of abbreviated handbooks. It brings together a great deal of information about compounds and reagents which biochemists use in their everyday research; and this has been achieved without producing an unwieldy tome. More

than half the book consists of a table of biochemical compounds, which is subdivided into nineteen alphabetically arranged sections. The first section deals with 182 aminoacids, peptides, and related nitrogenous compounds; the second with 151 carboxylic acids, alcohols, aldehydes, and ketones; the third with 127 phosphate esters, including nucleotides; the fourth with purines, pyrimidines, and nucleosides; the fifth with the spectral data and pK values for the compounds described in the fourth section, adding those of the nucleotides; the sixth with 77 carbohydrates and related compounds; and other sections deal with lipids and fatty acids, steroids, vitamins, porphyrins, chlorophylls, enzyme inhibitors, metal chelating agents, anti-metabolites, and so forth. Wherever appropriate, the following data are given for each compound: name, pseudonym, if any, structural formula, molecular weight, physical form, melting-point, optical activity, pK, solubility in water and organic solvents, references for preparation and estimation, and " general remarks ".

The rest of the book tabulates enzymes used as laboratory agents, buffers, and physiological media, methods for the detection of biochemical compounds on paper, properties of ion-exchange resins, isotopes, manometric techniques, ammonium sulphate solutions, pH indicators, normal solutions, temperature, pressure conversions, and atomic weights. There is an extensive index which can be used as a guide to the different tables.

The editors, research-workers in Oxford and Cambridge, have skilfully welded the various contributions into a work which will undoubtedly become a standard volume in biochemical laboratories all over the world.

A Short History of Nursing

W. R. BETT, M.R.C.S., F.R.S.L. London: Faber & Faber. Pp. 125. 12*s*. 6*d*.

NURSING is, perhaps, the most practical of all aspects of medicine. Textbooks and theoretical instruction are relatively less important for the nurse in training than for the medical student. And it is significant that, when that indefatigable penwoman, Florence Nightingale, addressed herself to her colleagues, in her *Notes on Nursing*, even she rested content with less than 150 pages. It is also a very ancient calling and there is no doubt that such an authority as Dr. Bett could write, if he wished, a treatise on its history running to several volumes. But he has very wisely restricted himself to a slender book of the same dimensions as Miss Nightingale's, written with a flair and a brevity that will ensure its being read throughout the sorority. Apart from its main theme, his little book deals with the history of such things as the nurse's uniform, the instruments she commonly uses, and her diet. Even the most practical members of a practical profession will enjoy this brief excursion into its bibliography.

The Ætiology and Arrest of Pre-eclamptic Toxæmia with Early Ambulant Treatment

K. DOUGLAS SALZMANN, M.D., M.R.C.P.E., D.OBST., practitioner-in-charge, Dellwood General Practitioner Maternity Unit, Reading. London: H. K. Lewis. 1960. Pp. 69. 10*s*. 6*d*.

IN 1955 Dr. Salzmann [1] suggested that eclampsia was caused by maternal reaction to transplacental hormones from a fœtus or hydatidiform mole. He believed that there was first a reaction against these hormones and this led to placental damage and the release of products which in turn caused toxæmia and eclampsia. The theory was little criticised at the time. In this volume the author is not so much concerned with ætiology as with the early detection and prevention of pre-eclamptic toxæmia. He is firmly convinced that the basic problem in toxæmia is vasospasm and that the first evidence of this is a slight elevation in diastolic blood-pressure. A rise of diastolic pressure above 84 mm. Hg is indicative of vasospasm and much of this short monograph is concerned with the place of reserpine in the management of these cases. He claims that the early use of reserpine by lowering the diastolic pressure and overcoming vasospasm prevents placental ischæmia and damage, and reduces the risk of toxæmia. From the trial he has conducted Dr. Salzmann argues that reserpine arrests the development of toxæmia in its earliest stages and in this respect is more efficient than bed rest. Emphasis is also placed upon the reduction of carbohydrate in the diet when the diastolic pressure is raised.

Dr. Salzmann produces many ingenious arguments in support of his theories but does little to help the reader sort out fact from fiction. Many statements are unsupported and it would be helpful to have the relevant references to the literature. Pygmies are said to have a high-protein/low-carbohydrate diet and not to suffer from toxæmia. Tall women with heavier babies are said to suffer more frequently from toxæmia and eclampsia, but this statement is not borne out by the studies of Nelson.[2] Dr. Salzmann repeats the commonly held view that eclampsia is more common in certain areas than others. While this may, indeed, be correct, Nelson is undoubtedly right when he claims that the truth of this statement remains to be tested.

In spite of these reservations, it is obvious that the author has thought a great deal about toxæmia, and obstetrician and physician will find much of interest in this book.

1. Salzmann, K. D. *Lancet*, 1955, ii, 953.

The Functions of the Endocrine Glands

PETER F. HALL, M.D., M.R.C.P., assistant physician, Sydney Hospital, and assistant lecturer in physiology, University of Sydney. Sydney: Horwitz. London: Pitman Medical Publishing Co. Philadelphia: W. B. Saunders. 1959. Pp. 290. 70*s*.

THIS book is written primarily for those interested in physiology, but with the increasing importance of physiology as a basis of clinical medicine, particularly in endocrinology, it should also be of considerable value to clinicians. It starts with a general account of the chemistry of hormones and their modes of action, which can easily be understood with the minimum of basic knowledge. Subsequent chapters deal with individual endocrine glands and related nervous mechanisms. Each chapter includes sections on embryology, anatomy, and histology (only those aspects strictly related to function) and on the biosynthesis of hormones, the control of their secretion, their actions, metabolism and fate in the body, tests of function, and the application of physiology in terms of disease.

The book is well written and readable and the layout is good, with clear headings and sufficient tabulation to enable the reader to extract the information he requires, without oversimplification. Subjects which are controversial or are not fully understood are discussed intelligently without introducing so many conflicting ideas as to confuse the reader. In the chapter on the adrenal cortex the physiological actions of the corticosteroids are not clearly differentiated from their pathological and pharmacological effects. The book is lavishly illustrated with chemical formulæ and diagrams, many of which are borrowed from works of leading authorities. There is a short but well-chosen bibliography at the end of each chapter.

British National Formulary, 1960 (London: British Medical Association and Pharmaceutical Press. 1960. Standard edition. Pp. 272. 7*s*. 6*d*. Interleaved copies 16*s*. 6*d*.).—Many new preparations have been added and some familiar but now seldom prescribed ones have had to be excluded. The lists of equivalent preparations and those with analogous therapeutic effect have been combined into one comprehensive glossary. The invaluable Notes for Prescribers at the beginning of the *Formulary* have been revised. A revised Alternative Edition, based on a pharmacological classification, will appear shortly.

The Merck Index of Chemicals and Drugs (7th ed. Rahway, N.J.: Merck & Co., Inc. 1960. Pp. 1641. $12).—The new edition of this valuable index contains nearly 10,000 descriptions of individual substances, more than 3300 structural formulæ, and about 30,000 names of chemicals and drugs alphabetically arranged and cross-indexed. There is now a separate and much expanded cross-index section of more than 30,000 names, which makes the pursuit of a substance much less arduous.

2. Nelson, T. R. *J. Obstet. Gynæc. Brit. Emp.* 1955, **62**, 48.

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Placenta Prævia

In Western Europe and the U.S.A. the number of maternal and fœtal deaths associated with placenta prævia fell dramatically in the first half of this century. Nowadays this condition rarely causes a maternal death, and the fœtal loss has dropped from 60 to 10%. Better maternal health, increased provision of antenatal beds, the development of an efficient blood-transfusion service, and the increased safety of cæsarean section have all contributed to the steady improvement.

In the management of this serious complication of pregnancy a big step forward was taken in 1945 when JOHNSON [1] and MACAFEE [2] showed that expectant treatment, by prolonging the pregnancy, greatly improved the outlook for the child without increasing the risk to the mother. Their claims have been confirmed by many in different parts of the world, and expectant treatment is widely practised. Nevertheless the correspondence that has followed Professor MACAFEE's article in our columns [3] shows that there are still unsettled issues in the management of placenta prævia. Most of the correspondence has been concerned with placentography. The accuracy of the technique has not been questioned; and this is not surprising, for REID,[4] WHITEHEAD,[5] HARTLEY,[6] LINDSAY,[7] and others have clearly demonstrated the precision with which a skilled radiologist can name the placental site. Opinions differ, however, as to whether placentography offers the clinician any real help in his management of the individual case. MACAFEE [3 8] believes that the case for placentography has been overstated, and his argument is strengthened by the knowledge that the excellent results he reports from his unit in Belfast are achieved without the help of radiology. He is supported by STALLWORTHY,[9] THEOBALD,[10] BROWNE,[11] WILLIAMS,[12] and VARTAN.[13] On the other hand, certain obstetricians, working closely with radiologists, are convinced that placentography has an important part to play in the management of placenta prævia. PERCIVAL and MURRAY [14 15] and WATSON et al.[16] hold that, once placenta prævia has been excluded by radiography and bleeding has ceased, patients who have had a small non-toxic accidental hæmorrhage need not be kept in hospital. This represents a saving in antenatal beds and must be a considerable relief for those patients who are allowed home. PERCIVAL and MURRAY have not so far had cause to regret discharging these patients from hospital, but it would be of interest to learn the experience of other centres.

PERCIVAL [14] and WATSON [16] and their colleagues have further established that placentography can reveal placenta prævia before bleeding has taken place. Both groups emphasise that the hazards of digital exploration of the lower uterine segment can be avoided altogether when radiography confirms the clinical impression that there is a major degree of placenta prævia. (Under these circumstances elective cæsarean section is carried out.) This point is very important; for any experienced obstetrician will acknowledge that, despite the greatest care, digital examination of the cervical canal and lower uterine segment may set off torrential hæmorrhage; and even today blood-transfusion is not without risks. RUSSELL and WARRICK [17] have shown how radiology can enhance the precision of surgical technique when a lower-segment section is performed for anterior placenta prævia. With the help of radiology the obstetrician is better able to avoid the bulk of the placenta and, therefore, less likely to damage the fœtal circulation.

Other methods of locating the placental site have been tried from time to time. Techniques involving cystography, aortography, retrograde catheterisation of the femoral artery, radioactive isotopes, and amniography have been described; but none except amniography has found much favour in this country. BURKE [18–20] has persistently advanced the case for amniography. One great disadvantage of this procedure is that the patient invariably goes into labour shortly after the contrast medium has been injected into the liquor.

Since the work of STEWART et al.[21] on leukæmia in childhood and its possible relation to antenatal X-ray examination, obstetricians have been more selective in their use of radiology; but it would be unfortunate if this caution were carried too far. The Adrian Committee [22] declared that there should be no hesitation in undertaking such investigations as placentography and pelvimetry when these are indicated. On balance placentography, correctly used, can probably contribute significantly to the management of cases of antepartum hæmorrhage, particularly when the placenta lies in the lower uterine segment.

The many manipulations previously applied at delivery were designed to save the mother's life, often at the expense of the fœtus. Valuable in their day, these procedures have now given way to cæsarean section, and most clinics report that 60–70% of their patients with placenta prævia are delivered abdominally. In modern obstetric practice lower-segment section is preferred, even when the placenta lies in the lower uterine segment; but this operation is not without risk

1. Johnson, H. W. *Amer. J. Obstet. Gynec.* 1945, **50**, 248.
2. Macafee, C. H. G. *J. Obstet. Gynæc. Brit. Emp.* 1945, **52**, 313.
3. Macafee, C. H. G. *Lancet*, Feb. 27, 1960, p. 449.
4. Reid, F. *Brit. J. Radiol.* 1949, **22**, 81.
5. Whitehead, A. S. *J. Fac. Radiol., Lond.* 1953, **4**, 245.
6. Hartley, J. B. *Brit. J. Radiol.* 1954, **27**, 365.
7. Lindsay, D. W., Davidson, J. K. *J. Obstet. Gynæc. Brit. Emp.* 1956, **63**, 828.
8. Macafee, C. H. G. *Lancet*, April 2, 1960, p. 773.
9. Stallworthy, J. *Proc. R. Soc. Med.* 1959, **52**, 565.
10. Theobald, G. W. *Lancet*, April 23, 1960, p. 921.
11. Browne, F. J. *ibid.* May 7, 1960, p. 1023.
12. Williams, L. *Proc. R. Soc. Med.* 1959, **52**, 564.
13. Vartan, K. *ibid.* p. 565.
14. Percival, R., Murray, S. *Lancet*, 1955, i, 1045.
15. Percival, R., Murray, S. *ibid.* March 12, 1960, p. 596.
16. Watson, H. B., Israelski, M., Jordan, W. M. *Brit. med. J.* 1957, ii, 490.
17. Russell, J. K., Warrick, C. K. *Lancet*, 1955, i, 785.
18. Burke, F. J. *J. Obstet. Gynæc. Brit. Emp.* 1935, **42**, 1096.
19. Burke, F. J. *ibid.* 1956, **63**, 771.
20. Burke, F. J. *ibid.* 1957, **64**, 596.
21. Stewart, A., Webb, J., Giles, D., Hewitt, D. *Lancet*, 1956, ii, 447. Stewart, A., Webb, J., Hewitt, D. *Brit. med. J.* 1958, i, 1495.
22. Radiological Hazards to Patients: interim report. H.M. Stationery Office, 1959. See *Lancet*, 1959, i, 975.

for the fœtus. In opening up the lower segment the operator, if he encounters placenta, may damage the fœtal circulation and the baby may die from exsanguination. NELIGAN and RUSSELL,[23 24] who studied this hazard carefully for some years, showed that, in operating for placenta prævia, the obstetrician will find placental tissue anteriorly in 40% of cases. With care the operator can usually avoid serious damage to fœtal vessels, but occasionally sufficient fœtal blood will be lost to threaten the life of the child. Where placenta is encountered NELIGAN and RUSSELL look carefully for damage to fœtal vessels, and in certain cases carry out serial skin-prick hæmoglobin checks on the baby; if the hæmoglobin falls below 90% (13·3 g. per 100 ml.) a blood-transfusion is given. The importance of their contribution is, first, that the operator can largely avoid the accident of fœtal blood-loss if he is aware of it, and, secondly, if there has been serious blood-loss the child's life can be saved by prompt transfusion.

In England and Wales during the three years 1952–54 twenty-nine women with placenta prævia lost their lives,[25] and in most cases hæmorrhage was the sole cause of death. The number of deaths is small; but it must be remembered that these were women in the prime of life—often with young families. In the prevention of such deaths there is no substitute for clinical experience. For example, the obstetrician, faced with hæmorrhage and difficulty in removing the placenta at cæsarean section, must recognise the occasional placenta accreta and know when to proceed without hesitation to hysterectomy. MACAFEE [3] rightly draws attention to this difficult situation, in which delay may prejudice the mother's chances of survival. In any event cæsarean section for placenta prævia should not be undertaken until cross-matched blood is available in the operating-theatre; and it is wise to set up an intravenous saline drip before anæsthesia is induced.

Fœtal mortality associated with placenta prævia is still 10% in our leading maternity hospitals; and the figure for the whole country is probably higher. This serious loss of fœtal lives remains a challenge to all branches concerned with maternity—including family practice, obstetrics, pædiatrics, radiology, and the blood-transfusion service.

Immunisation Against Tetanus

ON a later page of this issue Dr. G. E. FULFORD records that for England and Wales the Registrar General's returns show about 200 cases of tetanus a year, with a case-mortality of 27%. The much improved case-mortality (it was 50% in the period 1931–41) and the relatively small number of cases must not be made an excuse for neglecting the effort needed to rid ourselves of this eminently preventable disease. The true figures are likely to be higher than those in the official records, because some deaths will be certified as due to accident. There is a disproportionately high incidence among children of school age, especially in rural areas. The illness is a painful and distressing one, and each death an avoidable tragedy. Moreover, there is a great deal of anxiety among thoughtfully anxious parents and young casualty officers about whether they have perhaps failed to identify a wound carrying a risk of tetanus. Even the most careful parental and clinical care cannot eliminate anxiety of this kind. The original injury is often trivial and may even escape notice.

Passive immunisation, which involves injecting into the injured patient a dose of antitoxic serum from an actively immunised horse, confers immediate but rather brief protection lasting about two to three weeks; if the patient has previously had horse serum for any reason, protection may be very brief—a week or less—and the injection may induce severe anaphylaxis. A great deal of passive immunisation against tetanus is carried out in this country. BOYD [1] has cited CONYBEARE's estimate that 750,000 doses are given each year, resulting in perhaps 50,000 cases of serum sickness with a few dangerous anaphylactic reactions.

The surest way of preventing the anxieties, distresses, and deaths from tetanus, and the complications of passive immunisation, is to adopt a programme of active immunisation of children, combined with a method of recording the immunisation which will mean something to the casualty officer. Active immunity is produced by subcutaneous infection of three 1 ml. doses of tetanus toxoid, the second six to twelve weeks after the first. Immunity is established a few days after the second injection, but a third injection is required six to eighteen months later. Thereafter a dose of 1 ml. every five years will keep the immunity at a sufficient level. A patient so immunised needs no antitoxin if he is wounded, but he may be given a dose of toxoid. Obviously this ideal will not be attained without some trouble; some very rare persons fail to produce antitoxin; and there are some particularly dangerous wounds, such as a penetrating injury to a man spreading dung on a field. For these reasons, and perhaps for others, prophylactic antitoxin could probably not altogether be dispensed with even if active immunisation were generally accepted and fully recorded. But certainly we could very nearly eliminate both tetanus and the complications of its serum prophylaxis by persuading all concerned to adopt active immunisation and useful recording. But what is involved? In Putney, Dr. FULFORD found that only about a fifth of the public had been actively immunised at some time. This proportion will almost certainly fall when National Service ends; and the best hope lies in immunisation in early childhood and at school entry.[2] Hospitals could help by offering active immunisation to all who have received a wound of any kind; those who required antitoxin should have their active immunisation later, as in the scheme lately described by GARDNER.[3] Certainly such an effort would be worth making; but experience of public indifference to not very obvious dangers will prevent any great optimism about the

23. Neligan, G. A., Russell, J. K. *J. Obstet. Gynæc. Brit. Emp.* 1954, **61**, 206.
24. Neligan, G. A., Russell, J. K. *Brit. med. J.* 1955, i, 164.
25. Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952–1954. H.M. Stationery Office, 1957. See *Lancet*, 1957, ii, 375.

1. Boyd, J. S. K. *in* Symposium on Immunization in Childhood; p. 84. Edinburgh, 1960.
2. *ibid.*, see facing p. 128.
3. Gardner, P. A. *Brit. med. J.* April 23, 1960, p. 1277.

outcome. The only record of active immunisation that would provide sure information for the guidance of the casualty officer seems to be a tattoo mark. Record cards and disks would be satisfactory only if they were carried—and experience shows that this should not be expected. In short, we continue to have tragedies from tetanus because cases are too few to scare us into accepting the minor inconveniences of seeking active immunisation for ourselves and our children. It is easy to see why we are the despair of rationalists.

Lunar Journey

WE are so accustomed to artificial Earth satellites that an orbit no longer arouses a sense of wonder. Newspapers have lost interest in mere circumnavigation in space: this is a measure, not of public indifference, but of the speed of technological progress; and it seems certain we shall one day see a vehicle able to lift a man's weight to the moon and back.

Whether a man could survive the journey is another matter. Plans are well advanced in both Russia and the U.S.A. for the first step in human space travel. In Russia the latest step—an impressive one—has been the launching of a "spaceship satellite" weighing no less than $4^1/_2$ tons. In their "Project Mercury", the Americans expect to fire a man into orbit and bring him back after three circuits of the Earth. The physiological problems involved in such orbital flight are mainly the familiar ones of current practice in aviation medicine. The acceleration phase after launching is well within human tolerance; and, in a vehicle designed to reach orbital velocity, simple precautions such as correct posture and restraint are protection enough. The physiological measures necessary in the low barometric pressure at which military aviators fly are effective where there is no atmosphere at all, and any difficulty in providing a suitable environment is technological. The man in a space vehicle must have a cabin pressure sufficient to prevent decompression sickness, and he must wear a full pressure suit to protect him in case the cabin pressure should fall. So long as there is no fall in pressure his mobility and comfort are not greatly impeded since the suit need not be inflated; but his body surface must at all times be artificially ventilated, because pressure suits are made of fabrics through which water vapour cannot pass. Proper breathing mixtures must be supplied to his lungs whether his pressure suit is in use or not; and the temperature and humidity of the cabin atmosphere must be controlled within reasonable limits. He must have a chance of escape if things go wrong, at least from the time his vehicle is launched until it leaves the atmosphere and again when it returns to Earth. The technological difficulty of all this is simply that the space craft, unlike an aircraft, which maintains cabin pressure by compressing the atmospheric gases, must carry everything within itself—and this in a situation where weight is critical. Moreover a most exacting degree of internal temperature control is needed. As a satellite orbits from sunlight to shade, its surface temperature changes over a range of several hundred degrees: as it returns to the Earth's atmosphere it is heated to more than a thousand degrees by the sudden rise in friction.

About some aspects of orbital flight little is known. The phenomenon of weightlessness can be experienced for half a minute or so in certain aerobatic manœuvres. It is difficult to swallow dry food or to take liquids without inhaling them; and there is evidence that urinary urgency is diminished. But of the more dangerous effects which prolonged weightlessness may bring—severe disorientation perhaps, and hallucinations—not much is known. Many pilots flying alone at great altitudes are conscious of a sensation that all contact with the Earth has gone, that the aircraft has stopped in mid-air and will fall out of control if any manœuvre, however gentle, is attempted, and that the instruments have ceased to register the conditions of flight. This sensation can lead to panic. It arises, no doubt, from the absence of sensations normally associated with flight at lower altitudes, from the silence of the pressure cabin, the smoothness of the air, the lack of visual references outside the aircraft, and the remoteness from Earth. It has been called the "break-off phenomenon" and is probably related to the sensory deprivation states now receiving so much attention[1]; and it may well affect and disable a susceptible space traveller. It remains to be seen whether any form of selection can eliminate the susceptible or any form of artificial stimulation replace the familiar sensations of terrestrial life.

Least of all is known about what may prove to be the greatest hazard of space flight. The Earth's atmosphere acts as an efficient shield against the primary cosmic radiation, which is not encountered below 75,000 ft. Above it a man will be exposed to immensely energetic particles which are capable of producing ionisation in human tissues. Some of them—the heavy primaries—seem able to cause actual focal damage towards the end of their path. At orbital altitudes the risks of ill effects may be small, especially if the orbit is in an equatorial plane; for the Earth's magnetic field, which is greatest at the equator, deflects the cosmic radiation.

The "Mercury" orbit height is likely to be between one hundred and two hundred miles, and the sortie to last about four and a half hours: the distance to the moon is a quarter of a million miles, and the journey there and back must take more than a day. The speed necessary for orbit is 18,000 miles an hour: to escape to the moon it is a third as great again. The provisions for a man's welfare on a lunar flight are bound to be more elaborate. The supply of gases, absorbants, and refrigerants for the pressure cabin, of food and drink for the pilot, of electric power for control and communications—all are considerably increased. Acceleration and deceleration values are greater either in magnitude or in duration. The mental strain of the longer flight through the silent, empty regions may test any man's fortitude; and there is an added radiation hazard, not only from the longer exposure, but from the Van Allen belts of high-intensity radiation which almost surround the Earth. Yet once

1. See *Lancet*, 1959, ii, 1072.

manned orbital flight has been achieved, these difficulties should not be insuperable and may be met by development of existing techniques. Biological systems for respiratory-gas exchange, food synthesis, and recycling of urine may prove necessary for space flights lasting months or years. The radiation hazard is more difficult to assess, but even the Van Allen belts appear incomplete and may be avoided by a polar escape route.

For all its serene beauty, the moon seems to be a desolate place: deep wide valleys and high mountains exposed to the whole radiation spectrum, to micrometeorite bombardment, and to temperature changes from 212°F to −243°F; days and nights a fortnight long; an ambient pressure of 10^{-13} part of an atmosphere. The explorer may find some shelter in deep caves, but he will have to wear his pressure suit and carry with him an oxygen supply wherever he goes—not a great burden in the moon's low gravitational field. Even in this inhospitable climate there may be life of sorts, and it would be prudent to ensure that a returning spaceship brings back no unwelcome lunar guests in the shape of micro-organisms able to multiply on earth. Desolate though the lunar scene may be, and however long and hazardous the journey, there seems to be no fundamental physiological bar to success. The legends of the nursery are about to give way to the achievements of science.

Annotations

AGREEMENT ON HUMAN CHROMOSOMES

ONE summit conference which has reached a most welcome and complete measure of agreement is that which met last month in Denver to settle the nomenclature of human chromosomes. The system agreed upon was described in our last issue (p. 1063), and there seems every prospect that it will be accepted as a standard system.

It is only recently that we have been able even to count human chromosomes, and the identification of individual pairs is still a matter of considerable difficulty. The earliest anomalies to be described concerned only the X and Y chromosomes and the second smallest autosome pair (the " mongol " chromosome, now no. 21), and very little difficulty arose over the nomenclature of these. But as other rarer defects come to be described,[1–4] involving other chromosomes and possibly more than one at a time, precision becomes essential: all the more so when there exists the possibility of disagreement over the interpretation of some cases.

Independent groups of workers have evolved, as their studies progressed, various systems of nomenclature. Most have been based on a numerical system, arranging the chromosomes in order of length. The system with which most people in this country are familiar, that of Ford, Jacobs, and Lajtha,[5] is in one respect an extreme example of this, for it includes the X chromosomes in the series. Alternatively, one may emphasise the grouping of chromosomes, as is done in the system used by the French workers who first described the extra chromosome of mongolism.[6] The latter is in some ways the more natural system: in practice, one begins analysing a mitosis by first separating the groups, the biggest (1–5), the " wish-bones " (the blessedly characteristic groups of three pairs, 13–15, near the middle range of size with the centromere very near the end), and the smallest acrocentrics (21, 22, and Y) coming out relatively easily. Ford et al.'s system was affected by the grouping tendency; the chromosome pair now called 16 appears on their list in an anomalous position because they wished to group it with the much smaller pairs 19 and 20 on a basis of arm ratio. In the event, it has been decided to adopt the criterion of length almost exclusively, the autosomes being numbered from 1 to 22 entirely on this basis (save for some irregularity in the wish-bones 13–15, possibly dictated by the order of prominence of satellites), but leaving out the sex chromosomes, labelled separately as X and Y. The new system corresponds exactly to none of its predecessors, though it is nearest to that of the Uppsala group.

It is almost certainly the best system that could be devised at present. The group which worked it out consisted of representatives of all the teams of workers who had up to March of this year published detailed analyses of human mitoses. Seventeen members (eight American, four British, three Swedish, one French, and one Japanese) were invited to Denver by the University of Colorado. It is very encouraging to find that so diverse a group were able to reach agreement so quickly. It is to be hoped that other workers entering the field will endeavour to adhere to the new convention. So far as possible, we hope our contributors will use it, or, if they prefer, supply a key to their own system in terms of the new standard.

The new system lacks a good label: it cannot be identified by any one author's name. May we suggest that, in gratitude to the hosts of last month's meeting, it should be called the Denver system, and that chromosomes identified on this system be called, for instance, pair no. 16 (Denver)?

1. Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Clarke, C. M., Berg, J. M. *Lancet*, April 2, 1960, p. 721.
2. Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* p. 724.
3. Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, M., Wolff, O. H. *ibid.* April 9, 1960, p. 787.
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TUMOURS OF SALIVARY GLANDS

THE results of the treatment in Saskatchewan Province of 129 cases of tumour of the salivary glands have been reviewed by Prof. E. M. Nanson in a Hunterian lecture.[1] The standard treatment was local removal followed by irradiation. 79 tumours were classified as " benign mixed tumours "—62 primary and 17 recurrent. 2 of the primary and 3 of the recurrent tumours had returned at the time of review. Professor Nanson compares these results with those in other recorded series in which the recurrence-rates were up to 40%, and he attributes the improved results in his series to routine irradiation. But what he cites as the recurrence-rates of some workers is the percentage of all cases with recurrence, including those with recurrence at the time of treatment—a percentage similar to that in his own series.

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Of another 17 cases classified as "malignant mixed tumours", 6 had recurred. It would have been interesting to know whether in any, and if so in how many, of these cases the diagnosis had been revised from an original one of benign mixed tumour as a result of the clinical behaviour of the tumour. If there were any such revisions, the recurrent cases might legitimately have been added to those of the benign mixed tumour group. In the other types of malignant parotid tumours the five-year mortality-rate was 20–60%.

Professor Nanson concludes with two appendices. In the first he describes in detail the operation of parotidectomy with preservation of the facial nerve, and concludes: "It is suggested that all tumours of the parotid gland should be removed by this method of radical anatomical surgery." In the second appendix he describes experiments in which atrophy of the parotid glands of rats was induced by heavy doses of irradiation—up to 8000r—and argues that these observations support the use of irradiation clinically as a supplement to the surgical treatment of salivary tumours.

DIAGNOSIS OF INFLUENZA-LIKE DISEASES

MANY different viruses are now known to be responsible for outbreaks of respiratory disease. Can these infections be distinguished clinically? Can we, for example, differentiate an illness due to influenza-A virus from one due to an adenovirus? This question has been explored, but the answers are not yet clear. In England, Fraser et al.[1] investigated influenza-like illnesses in Naval personnel admitted to hospital in the spring of 1959. Most had been infected by influenza A, influenza B, or adenovirus. Infections with influenza-A virus preponderated, the other viruses each being responsible for only about half as many cases. Influenza-B virus was responsible for a higher proportion of cases of pneumonia—20%, compared with 14% for influenza-A virus and 12% for adenovirus. Fraser et al. were unable to distinguish on clinical grounds alone between infections with the different viruses.

On the other hand Schultz et al.[2] in the U.S.A., working similarly with Naval patients in hospital, were able to distinguish the clinical picture due to Asian influenza virus from that due to adenovirus infection. In the summer of 1957 they studied 112 cases of influenza due to Asian type A, 64 cases of adenovirus infection, and 34 cases of unknown ætiology. The patients in this third group had diseases resembling influenza but with a higher incidence of pneumonia; this group was almost certainly not homogeneous and contained infections caused by several different organisms.

These studies, and similar ones among Air Force personnel, suggest that prolonged combined clinical and ætiological investigations may provide enough experience to enable us to recognise from the symptoms of groups of patients what sort of virus is responsible for an epidemic of respiratory disease. In the case of any single patient, however, it will probably never be possible to guess the causal organism from the clinical picture.

So far the investigations have usually concerned special groups of people—schoolboys, soldiers, sailors, and airmen. Equivalent studies should be undertaken on the common outbreaks in the homes of ordinary citizens. There is a case for establishing permanent observation-posts whose main duty would be to characterise every epidemic that visited the area. Only in this way will it be possible to accumulate the evidence from which to form a reliable conception of the biology of all the organisms that are leading their lives at our expense and continually disturbing the community life around us.

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2. Schultz, I., Gundelfinger, B., Rosenbaum, M., Woolridge, R., De Berry, P. *J. Lab. clin. Med.* 1960, **55**, 497.

DOMESTIC WORK IN HOSPITALS

THERE was a time when most of the duties of a probationer nurse were those of an overworked and underpaid domestic servant. Nowadays over £17 million is spent on domestic work in hospitals in England and Wales—and this figure takes no account of similar work done by portering staff and ward orderlies. Economic and social changes since the war have made the recruitment of domestic staff, of whom there are over 50,000, difficult; but a report from the Ministry of Health[1] shows that improvements are sometimes possible without increased numbers and at little or no additional cost. It is based on surveys made in National Health Service hospitals, supplemented by information from industrial and commercial concerns. The aims of the inquiry were those of time-and-motion study in industry—to find the volume and type of work done, the best way of doing it, the number of staff required, and (most important of all) the best ways of ensuring that nurses shall be free to concentrate on caring for the patients.

80% of the time spent on domestic work in hospitals is taken up on four tasks—30% of the time on cleaning and polishing floors; 15% on washing and scrubbing floors and walls; 10% on dusting and polishing furniture and fittings; and 25% on washing up crockery.

To be hygienic there is no need for floors to have a mirror-like surface; in fact, such floors, particularly if of thermoplastic tiles, may be dangerous to both patients and staff. The need for polishing wood and cork floors, and some types of linoleum, may be eliminated by the use of plastic floor seals which are non-slip and do not need waxing. In any event, some experts think that floors need be polished only three to five times, and then merely to preserve the surface. The tradition of polishing floors at least once a week is better forgotten. When floors have to be polished, the report recommends the use of power-driven machines, although the use of such machines for stone and similar floors is seldom justified.

For general dusting, especially at heights above eye level, vacuum-cleaners of cylinder type are recommended. Electric-light fittings often form dust-traps, and are equally often neglected. It is suggested that these should be the responsibility of the engineering or portering staffs rather than that of the female domestic staff.

Washing-up machines do not offer such advantage as may appear at first sight: much of the time wasted on washing up could be saved by intelligent planning on the lines laid down in a Government booklet, *Clean Catering*.[2] The use of drying cloths is deprecated because they are a potent source of infection; washing-up water should be sufficiently hot (at least 170°F, or 77°C) for crockery to dry rapidly on its own.

The report cites instances of wasted effort—such as the time spent in polishing odds and ends of metal that would be better painted over, and the enthusiasm devoted to the polishing of cutlery—particularly that for the use of senior staff—with unnecessarily large amounts of metal polish. Emphasis is rightly placed on the proper cleansing and disinfection of mops, brooms, and floor cloths.

1. Organisation and Management of Domestic Work in Hospitals. Hospital O and M Service Reports, no. 4. London, 1960. Pp. 30. 2*s*.
2. Clean Catering. H.M. Stationery Office. 1959.

The turnover of hospital domestic workers is high, mainly because of the competition from industry, and the report deals with the non-financial factors which contribute to good relations between management and staff, and includes suggestions for training and supervision. Domestic work in hospitals presents many problems, and, as correspondents pointed out last year, many of our hospitals are dangerously dirty. This report is a timely reminder that in the control of infection cleanliness is more important, and often cheaper, than polish.

DICHLORPHENAMIDE FOR RESPIRATORY INSUFFICIENCY

MUCH can now be done to tide the patient with chronic bronchitis and emphysema over an acute episode of respiratory insufficiency, but chronic hypoxia and hypercapnia tend speedily to exhaust therapeutic ingenuity. A favourable report by Naimark et al.[1] on the effect of dichlorphenamide in this condition is, therefore, welcome. Dichlorphenamide, a new carbonic anhydrase inhibitor with an activity estimated as 30 times that of acetazolamide, was given in a dosage of 200 mg. daily for from two to thirty weeks to 15 hospital patients with hypercapnia persisting after intensive routine therapy.

11 of these patients had emphysema, 1 had undergone thoracoplasty on account of pulmonary tuberculosis, 1 had kyphoscoliosis, and 2 had pulmonary fibrosis; all had clinical evidence of severe respiratory insufficiency associated with hypoxia and hypercapnia. With 1 exception these patients claimed to have less dyspnœa, greater effort tolerance, and a feeling of well-being while receiving the drug. Clinical improvement was associated with favourable changes in arterial gas tensions: there was pronounced reduction in hypercapnia in every patient but 1 (mean decrease 10·9 mm. Hg) and a consistent rise in oxygen tension (mean increase 16·3 mm. Hg). Side-effects were absent, except for transient nausea in 2 patients and severe headache in 1. Withdrawal of the drug was followed by clinical deterioration, increased hypercapnia, and hypoxia, and further administration by clinical recovery and more favourable arterial gas tensions. The alveolar oxygen tension rose in 7 out of 9 patients studied, and this change was accompanied by a rise in arterial oxygen tension although in 5 of these subjects the alveolar-arterial oxygen gradient increased: on the other hand, in 2 patients the arterial oxygen tension rose although the alveolar oxygen tension did not, so that in these the alveolar-arterial oxygen tension gradient decreased. Alveolar ventilation was increased in the 7 patients with a rise in alveolar oxygen tension: the mean increase was 0·67 litre per minute, and the mean increase in minute ventilation was 0·6 litre per minute. The respiratory rate tended to slow and the tidal volume to increase.

Significant diuresis during dichlorphenamide therapy was noted in only 2 patients, and the arterial pH after an initial fall tended to return to the control level. The effect of the drug on water and electrolyte excretion was specially studied in 3 patients. In 2 receiving the standard ward diet, administration of the drug resulted in significant diuresis with an increased output of sodium, potassium, and chloride associated with a fall in arterial pH, serum-bicarbonate, and serum-sodium and, despite the chloruresis, a rise in serum-chloride. The other patient was put on a fixed sodium-chloride intake, and here there was transient diuresis, an increased output of sodium and potassium, and very slight chloruresis; there was a fall in serum sodium and potassium and in arterial bicarbonate, a rise in serum-chloride, and a gradual rise in arterial pH to the control level after an initial fall.

Naimark et al. point out that the reduction in arterial carbon-dioxide tension during dichlorphenamide therapy could be accounted for by increased alveolar ventilation, decreased tissue carbon-dioxide production, or a combination of these factors. Alveolar ventilation did, in fact, increase in most patients, and, although changes in carbon-dioxide elimination or oxygen consumption were not observed, Naimark et al. do not exclude the possibility that they may have been present. The hypothesis of decreased tissue carbon-dioxide production is supported by the evidence that acetazolamide decreases the metabolic rate in rats.[2] Although the resting ventilation increased during dichlorphenamide therapy, the ventilatory response to inhaled carbon dioxide in 3 healthy and in 3 emphysematous subjects did not indicate heightened sensitivity of the respiratory centre to changes in arterial carbon-dioxide tension. But in dogs acetazolamide has been found to decrease elimination of carbon dioxide by increasing the body carbon-dioxide stores [3]; and Naimark et al. suggest that, owing to the carbonic-anhydrase-inhibiting effect of dichlorphenamide, the carbon-dioxide tension in the tissues and in the respiratory centre may actually have been higher than it was before treatment, thus accounting for the increased ventilation and the lowered arterial-blood level. They do not consider that relief of pulmonary congestion as a result of diuresis is likely to account for the improvement in gas tensions, for a significant diuretic effect was not demonstrated in most patients who were notably benefited by treatment.

Further investigation is obviously needed to determine exactly how dichlorphenamide works, but meanwhile the results of this interesting study strongly suggest that it will prove valuable in the management of chronic respiratory insufficiency.

HEALTH AND PRACTICE

Darbishire House is six years old, and without further description doctors throughout the world identify this active youngster as the child of Manchester University and the city of Manchester. A new pattern of medical care is being developed in centres such as this where practice, without (it is hoped) losing its personal character, is being adapted to the advances of the present day. At Darbishire House the general practitioner can work to the same standard of efficiency as his hospital colleague, and he can teach this standard to others. The student is taught that the practitioner's responsibility is towards the whole person—indeed the whole family—and that where he cannot himself fulfil this responsibility he should do so through the special skills of others who work with him. A full-time social worker is based on the Manchester unit; and the district nurses and midwives are also members of the practice team in whose work prevention and therapy merge.

If the idea of integrated preventive and therapeutic health care based on general practice is now accepted, the methods by which this is to be achieved are still far from settled. In centres such as Darbishire House different methods can be tested. Further operational research into the activities of general practitioners is urgently needed both in health-centre practices and in those of conventional type. The universities of Manchester, Edinburgh, and Bristol, each of which has developed its teaching health centre in its own way, have shown that the partnership between don and practitioner can be fertile. Others might usefully do the same.

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Special Articles

THE PREVENTION OF TETANUS *

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ACTIVE immunisation with tetanus toxoid was introduced twenty years ago. It was used extensively during the 1939–45 war and reduced the incidence of tetanus in the American army to 6 cases per million injured. The corresponding figure at the end of the 1914–18 war, using anti-tetanus serum, was 1000 cases per million injured (Barr and Sachs 1955).

In England and Wales there are now about 200 cases of tetanus every year, and in 1957 the number of deaths was 28 (Registrar General 1958). The case-mortality has steadily fallen from about 50% in 1931–41 to 27% in the past ten years. The number of deaths is highest in boys aged five to fourteen years, and most of them are in rural areas, particularly in East Anglia and the south-west (*British Medical Journal* 1955).

Moynihan (1956) estimated that in 15% of cases of tetanus the original injury was trivial, while in 35% it was unknown. Hence even the most careful use of anti-tetanus serum, given prophylactically, could prevent only half the cases—or perhaps less, because occasionally elimination of serum is increased (Barr and Sachs 1955) and tetanus may

TABLE I—DISTRIBUTION BY AGE-GROUPS OF MALES AND FEMALES IN THE SURVEY
Expected distribution in parentheses (Registrar General 1958)

Age-group	Males	Females	Total
0–4	61 (*54*)	28 (*20*)	89 (*74*)
5–9	122 (*58*)	73 (*25*)	195 (*83*)
10–14	114 (*49*)	48 (*20*)	162 (*69*)
15–19	86 (*43*)	19 (*19*)	105 (*62*)
20–29	98 (*90*)	24 (*39*)	122 (*129*)
30–39	85 (*99*)	37 (*43*)	122 (*142*)
40–49	64 (*104*)	31 (*45*)	95 (*149*)
50–59	24 (*87*)	19 (*40*)	43 (*127*)
60–69	23 (*60*)	20 (*32*)	43 (*92*)
70+	13 (*46*)	11 (*27*)	24 (*73*)
Total	690	310	1000

TABLE II—INCIDENCE OF DIFFERENT TYPES OF WOUNDS
Actual numbers in parentheses

Classification of injury	Males	Females	Total
Superficial	37% (*258*)	44% (*135*)	39·3% (*393*)
Deep	55% (*380*)	46% (*143*)	52·3% (*523*)
Penetrating	8% (*52*)	10% (*32*)	8·4% (*84*)
Clean	70% (*482*)	78% (*242*)	72·4% (*724*)
Dirty	30% (*208*)	22% (*68*)	27·6% (*276*)

then occur in spite of its administration (Littlewood et al. 1954).

Active immunity is produced by subcutaneous injection of three 1 ml. doses of tetanus toxoid, the second six to twelve weeks after the first. Immunity develops a few days after the second injection, but a third is required six to eighteen months later. Thereafter immunity can almost always be maintained by a booster dose of 1 ml. every five years. After wounding, a booster dose should be given unless the injury has occurred within six months of the second injection or within eighteen months of a third or booster dose, when the patient will be covered by the immunity from the last injection.

Survey

The object of my survey was to ascertain how the benefits of immunisation can best be given to the public. It was made in the casualty department of Putney Hospital where, within four months, 1000 patients were seen who had a breach of epithelium (not caused by burns). These formed the survey group (tables I and II).

Previous Prophylaxis

When the patient had had prophylactic treatment more than once, only the latest injection was recorded, except when serum had been given after active immunisation (table III).

156 patients (121 males and 35 females), or 16% of the series, had had serum. 175 (18%) had been actively immunised while in the Forces: of these only 3 were women and 104 had been immunised ten or more years previously. 14 had subsequently been given serum. Only 50 patients (5%), of whom 7 were females, had received tetanus toxoid outside the Forces.

TABLE III—PREVIOUS ANTI-TETANUS PROPHYLAXIS

—		1958	1957	1956	1955	1954	1953	1952	1951	1950	1949	1948–43	1943–	Total
Anti-tetanus serum	Male	17	30	24	13	10	6	3	1	4	1	7	5	121
	Female	1	12	3	3	1	4	3	3	..	..	2	3	35
Tetanus toxoid in Forces	Male	..	7	17	19	5	3	4	3	3	7	97	7	172
	Female	..	..	1	..	..	..	2	..	..	..	..	..	3
Tetanus toxoid from other sources	Male	25	8	5	2	2	..	..	..	1	..	..	..	43
	Female	3	3	..	..	..	1	..	..	..	..	..	..	7

10 children had had toxoid as part of their immunisation in infancy, while 1 had had it before going abroad with his soldier father. An ex-employee of the Southern Gas Board had been immunised while in the board's service. 2 men had been immunised in hospital as part of their treatment. One American lady had been immunised before starting on her tour of Europe. An Englishman was also seen who had been immunised before travelling abroad. The remaining patients had all received toxoid in a casualty department. 16 patients had had boosting doses (10 elsewhere and 6 at Putney Hospital), while 18 had received their first dose of toxoid at Putney (13 during the survey) and returned with a second wound.

Treatment

As part of the treatment every patient received some form of anti-tetanus injection unless he was covered by active immunisation or refused the injection (7) or was being immunised against poliomyelitis (20) (table IV). 19 of those who were held to be covered had been immunised in the casualty department of Putney Hospital as part of the treatment of a previous wound.

Anti-tetanus serum was given whenever there was much risk of tetanus—usually for penetrating wounds incurred out of doors. Before patients were given the full dose of serum they always had a test dose; and if this produced a general or local reaction the case was reassessed. Serum was not given to any patient who had had it previously.

94 test injections of serum were given with no general reactions, but 1 boy had a local reaction and did not receive the full dose, being actively immunised instead. The remaining 93 had full doses of serum with no immediate reactions, but 5

TABLE IV—ANTI-TETANUS PROPHYLAXIS GIVEN IN SURVEY

Treatment	Males	Females	Total
Serum test dose	54	40	94 (*9·4%*)
Serum full dose	53	40	93 (*9·3%*)
1st toxoid	412	259	671 (*67·1%*)
2nd toxoid	195	125	320 (*32·0%*)
	15 elsewhere	10 elsewhere	25 elsewhere
Booster toxoid	187	6	193 (*19·3%*)
Refused	7	..	7 (*0·7%*)
Receiving poliomyelitis immunisation	15	5	20 (*2·0%*)
Actively immune	25	4	29 (*2·9%*)

* From a paper successful in the South West Metropolitan Regional Hospital Board's competition for research report, 1958.

patients had a local reaction between the fourth and eighth day. In 1 this became a generalised urticaria which was only controlled with anti-histamines six weeks afterwards. The incidence of local reactions was therefore 6%, which agrees with the findings of Moynihan (1955). 14 of these patients returned for active immunisation, including 5 of the 6 who had had reactions.

The remaining patients received tetanus toxoid. For those who had been actively immunised previously this was a boosting dose. Those for whom it was a first injection were given a form telling them that they would require a second injection in six weeks. When they attended for this they were given a record of the immunisation.

Of 671 receiving a first injection 320 (52%) returned for the second. 35 said they would get their second injection elsewhere. In 4 cases there were local reactions to toxoid but these were less severe than the serum reactions. Of the wounds treated, 452 were sutured and 60 patients were given antibiotics.

Discussion

Because tetanus may follow trivial wounds, it cannot be completely prevented by a policy of passive immunisation.

This is vividly illustrated by a case at Putney soon after the end of the survey. An elderly lady sustained a small laceration of her leg while out in her garden on Guy Fawkes night. She would probably never have been seen except that the wound involved a varicose vein and bled excessively. Elevation of the leg stopped the bleeding and the laceration was treated by local toilet and dressing. A week later she was admitted with tetanus.

Tetanus can be eradicated only by active immunisation of the population. This is a formidable undertaking, but the survey shows how it can be done.

At Putney about a fifth of the public had already been actively immunised at some time, mostly in the Forces. Half of them, however, had been inoculated ten or more years previously, and after this time probably only about 60% of people have enough antibodies to prevent tetanus. On the other hand 99% will still respond to a boosting dose of toxoid and can produce an adequate antibody response by the thirteenth day (Peterson 1955). When treated for any wound, these people should always be given a boosting dose of toxoid.

14 patients had elsewhere been given serum though they had a history of active immunisation. In 3 of these cases (1 treated at a teaching hospital) serum had been given within three years of active immunisation. If a patient had died from one of these serum injections a charge of negligence might have been made.

Now that National Service is ceasing, the principal source of active immunisation will disappear, and the active immunity of the population will decrease. Some efforts are being made on behalf of certain sections. For example, many independent schools are immunising their children (Morley 1958, Scott 1958) and the Southern Gas Board offers active immunisation to all men employed on mains or service-laying gangs (Carson 1958). But, though such arrangements should be encouraged, their effects are small in relation to the population as a whole.

Another source of active immunity is immunisation of infants with combined antigens. Tetanus has been combined with diphtheria and pertussis, so that immunity to all three can be produced by three injections at monthly intervals. But most of this work is done at welfare clinics, which, on advice from the Ministry of Health (1957), have been giving each immunisation separately, because of the possible greater risk of poliomyelitis after the use of combined antigens (Medical Research Council 1956). In its first year a baby is thus given a large number of prophylactic injections of which tetanus is left until last—by which time the mother as well as the baby are tired of the needles, and tetanus immunisation is not performed.

The effect of this policy is shown in the survey; for, whereas about three-quarters of the children under ten years of age had been immunised against diphtheria or pertussis, only 6 patients, 1 of whom was Danish, had received combined antigens. If all these children had been given combined antigens, the number of actively immune patients in the survey would have been doubled. That infancy is the right time for tetanus immunisation is confirmed by the fact that our patients with wounds included four times as many young people (aged between five and nineteen) as the general population (table I), and the highest death-rate from tetanus is in boys aged five to fourteen. Lately, because of the increase in the number of immunising injections, clinics in some areas have begun to use combined antigens.

A further opportunity for active immunisation is in casualty departments. Already some departments are offering active immunisation to people who have been given anti-tetanus serum (Gardner et al. 1958, Randall 1958). In this survey, by giving toxoid to every patient who did not need serum, and by offering active immunisation after serum prophylaxis, 320 people were actively immunised, returning for their second injection. A very rough estimate of the population served by the Putney Hospital casualty department is 50,000, which means that about 0·5% of them were immunised in four months. If this policy was applied to the whole country 1·5% of the population would be actively immunised each year, and in adding these to the number already immune we should have gone a long way towards our aim of active immunity for everybody.

That this use of toxoid is worth while is shown by the fact that in these four months no fewer than 13 patients returned with fresh injuries, having been actively immunised earlier in the survey.

The main objection to active immunisation is that people rarely know the details of their previous immunisations, and without this information a doctor cannot know whether a patient will be protected immediately by a further single injection of toxoid. One answer to this is that everybody should carry a record card. Admittedly cards are lost, and not carried when required; and, as Kup (1958) pointed out, they would have to be made of a " highly durable and synthetic plastic " if they were not to wear out. These difficulties could be overcome by a central records department, which would maintain duplicates; but probably the cost will prevent this for many years. In this survey the only person who carried a record card of immunisations was an American.

This survey shows, I suggest, that in a given area tetanus can be best prevented by using only tetanus toxoid. To be effective this policy requires the cooperation of all medical practitioners and would perhaps need to be adopted at regional-hospital-board level.

Toxoid should be given to all infants, and also whenever a doctor (general practitioner or casualty officer) sees a patient with a breach of epithelium. A large section of the unprotected population will thus become actively immune and will be protected against tetanus following any injury. Moreover the immunity of those already immunised will be maintained.

Such a policy would reduce the morbidity from serum reactions. Eventually it would also abolish the need for record cards, because a history of previous injury or "anti-tetanus" injection would always imply the use of toxoid.

Meanwhile there will be a period when the number of people who have had toxoid will be rather small. This can be covered by giving toxoid to everyone who has, or may have, previously had any type of anti-tetanus injection. (At present these are about 40% of the population.) If it is certain that the patient has never previously had any such injection, then, on the merits of the injury, the doctor decides whether to give anti-tetanus serum or not. If he decides not to do so, the patient is given toxoid and should attend for a second injection in six to twelve weeks' time. All patients given serum are offered active immunisation six weeks afterwards. As an increasing proportion of the patients will have had an anti-tetanus injection of some kind, serum will be given less and less often prophylactically.

Summary

As a means of prophylaxis, anti-tetanus serum is unsatisfactory because it will never be used for all trivial wounds and because it can itself cause illness and occasionally death.

In a patient who has previously had serum, a prophylactic dose of serum may be ineffective.

All patients who have had serum should afterwards be actively immunised with toxoid.

In this country about a fifth of the population at risk have already been actively immunised, and this proportion could be rapidly increased by the general use of combined prophylactics for infant immunisation. The active immunity of the population could then be maintained by the general use of toxoid in casualty departments.

The need for recording immunisations can be overcome by adopting a standard procedure for all patients on wounding:

1. All patients who have previously had an anti-tetanus injection of any type are given tetanus toxoid.

2. If the previous injection was serum or inadequate primary active immunisation, the patient is asked to attend for a second injection of toxoid six to twelve weeks later.

3. Patients who have never had any anti-tetanus injection can be given serum or toxoid at the doctor's discretion. Afterwards they should be actively immunised by further injections of toxoid.

This procedure would very rapidly eliminate the prophylactic use of serum and produce a high level of active immunity in the population.

I would like to thank the other casualty officers and the nurses of the casualty department for their help with this survey.

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Occasional Survey

DIAGNOSTIC ENZYMOLOGY

SERUM-ENZYME levels are being determined increasingly often as an aid to diagnosis. In disease raised levels are occasionally due to release of these substances into the bloodstream from dead or damaged cells. Last year in a symposium on diagnostic enzymology the clinical significance of serum-alkaline-phosphatase,[1] serum-acid-phosphatase,[2] serum-transaminases,[3] and plasma-amylase[4] was discussed.

ALKALINE PHOSPHATASE

Robison's[5] discovery of alkaline phosphatase in bone stimulated investigation of the effect of skeletal diseases on the serum-alkaline-phosphatase. Raised levels were demonstrated in Paget's disease, hyperparathyroidism, rickets, osteomalacia, osteosarcoma over-productive of bone, and carcinoma with widespread skeletal metastases which are predominantly osteoplastic. It was soon realised that in each case the increases were associated with increased activity of osteoblasts. In Paget's disease the level tends to rise slowly with extension of the disease and more rapidly when osteogenic sarcoma develops. Differentiation of Paget's disease from the osteoplastic metastases of prostatic carcinoma is not aided by determining serum-alkaline-phosphatase, since high values are common to both. In hyperparathyroidism the level is usually raised but it may be within normal limits. The skeletal origin of the surplus serum enzyme is indicated by the fact that on removal of the parathyroid tumour the serum-alkaline-phosphatase level remains raised for a time, and may even rise further, before subsiding gradually over many months as bone repair slowly comes to a halt. In rickets due to malnutrition, the increase in the serum enzyme is usually the first index of active disease and is more sensitive than clinical or radiographic examination. The serum-alkaline-phosphatase level is usually normal with healing fractures, in osteopetrosis, and in generalised osteosclerosis due to chronic fluorine poisoning. It is usually normal, but may be increased, in other forms of osteosclerosis and in fibrous dysplasia of bone. Diseases characterised by osteoporosis or bone destruction are associated with normal serum-alkaline-phosphatase activity: a typical example is multiple myelomatosis.

In some diseases the serum-alkaline-phosphatase level may be lower than normal. Low levels are found with arrest of growth—for example, in achondroplasia or cretinism. The level is low also in scurvy and after exposure to radioactive substances which are deposited in the bone.[6] Hypophosphatasia[7] is an interesting clinical syndrome due to an inborn error of metabolism characterised by deficiency of alkaline phosphatase in bone, kidney, intestinal mucosa, liver, leucocytes, and blood-plasma. The syndrome is dominated by abnormal mineralisation of bone which may result in profound skeletal changes closely mimicking vitamin-D-resistant rickets.

Alkaline phosphatase is probably excreted mostly

1. Gutman, A.B. *Amer. J. Med.* 1959, **27**, 875.
2. Woodard, H. Q. *ibid.* p. 902.
3. Wróblewski, F. *ibid.* p. 911.
4. Janowitz, H. D., Dreiling, D. A. *ibid.* p. 924.
5. Robison, R. *Biochem. J.* 1923, **17**, 286.
6. Aub, J. C., Evans, R. D., Galagher, D. M., Tibbetts, D. M. *Ann. intern. Med.* 1938, **11**, 1443.
7. Rathbun, J. C. *Amer. J. Dis. Child.* 1948, **75**, 822.

through the biliary tract.[8] It is, therefore, not surprising that both intrahepatic and extrahepatic obstruction of the biliary tract are associated with a rise in the serum level. Thus a rise is found in space-occupying hepatic lesions, such as metastases and abscess; in granulomatous and infiltrative diseases of the liver, such as sarcoidosis, tuberculosis, Hodgkin's disease, and amyloidosis; in drug-induced hepatotoxicity of the cholestatic type (such as is caused by arsphenamine and chlorpromazine); and in obstruction due to biliary cirrhosis. There is a larger obstructive element in viral hepatitis; but in the majority of patients with this disease the increase in serum-alkaline-phosphatase activity is distinctly less than is usual in obstruction of the extrahepatic or intrahepatic biliary tract. This has not yet been satisfactorily explained.

ACID PHOSPHATASE

As regards serum-acid-phosphatase,[2] a cardinal feature is that adult human prostate contains up to 1000 times the activity of other tissues, but this high activity does not appear until puberty. In health the serum contains a small but significant amount of acid phosphatase of unknown, non-prostatic, origin; but the amount is greatly increased in the majority of men with metastases from prostatic carcinoma, in whom the level falls sharply within three or four days after surgical castration or within two weeks after the institution of œstrogen therapy. Patients whose acid phosphatase does not decrease significantly during endocrine therapy fail to remit clinically. The serum level rises irrespective of whether metastasis has taken place to bone or to the soft parts. The most probable explanation of these findings is that the intact gland contains barriers which ordinarily prevent escape of the enzyme into the circulation, but when metastasis takes place these barriers are no longer present and the prostatic secretion enters the blood. About a quarter of untreated patients with disseminated disease have no clear-cut increase of serum-acid-phosphatase.

In health, acid phosphatase activity is about the same in the serum of women as in that of men. Likely sources of the enzyme normally present in the blood are liver, red blood-cells, and blood-platelets. Obviously, therefore, acid phosphatase from diseased tissues besides the prostate may enter the circulation in measurable amounts. Raised serum levels have occasionally been reported in cases of Paget's disease of bone, of metastases, and of hyperparathyroidism; and the level is often raised in Gaucher's disease.[9] It is therefore important to differentiate acid phosphatase derived from the prostate from that derived from other tissues. This is done by means of differential inhibition. Ethyl alcohol and *l*-tartrate apparently have a rather selective inhibitory effect on prostatic acid phosphatase and little effect on the acid phosphatase of erythrocytes; the reverse is true of cupric ions and formaldehyde, which inhibit erythrocyte phosphatase notably, but prostatic phosphatase very little. Using acid phosphatase inhibition by *l*-tartrate, Fishman et al.[10] have demonstrated increases in prostatic acid phosphatase in the serum of healthy men after massage of the gland. Accordingly, examination of the serum for this enzyme should not be preceded by manipulation of the prostate either manually or by catheterisation. It seems that some 6% of healthy men have transitory rises in serum acid phosphatase inhibited by tartrate,[11] and thus a slight rise is not a reliable index of prostatic cancer unless it is shown to persist.

TRANSAMINASES

Wróblewski,[3] discussing serum-transaminase determinations in the diagnosis of ischæmic heart-disease,[3 12] points out that a rise in serum-glutamic-oxalacetic-transaminase (S.G.O.T.) activity above 300 units, at the peak after infarction, indicates a poor prognosis. After myocardial infarction a rise in S.G.O.T. activity is not influenced by, or correlated with, heart-failure uncomplicated by liver disorder, location of the infarction, administration of digitalis or quinidine, age, sex, colour, body-temperature, erythrocyte-sedimentation rate, leucocyte-count, or urinary output. When the electrocardiogram is not diagnostic of myocardial infarction or is obscured by previous myocardial infarction, bundle-branch block, Wolff-Parkinson-White syndrome, or other electrocardiographic aberrations, a rise in S.G.O.T. activity in a clinical setting suggestive of infarction is especially helpful in diagnosis. Secondary rises have been observed in patients who, following acute myocardial infarction, show clinical features consistent with extension of the infarct. With regard to hepatic disease, ambulation during recovery from infective hepatitis is sometimes associated with a small rise in serum-transaminase; if the rise is 50 or more units, return to rest is recommended.[13] Deviations from the usual pattern of serial alterations in S.G.O.T. and serum-glutamic-pyruvic-transaminase in the course of acute infective hepatitis suggest associated complications, relapses, or chronicity of the hepatic lesion. Apparently the serial and quantitative changes in the serum-transaminases during the course of hepatitis reflect the clinical state more accurately than do the usual tests of liver function. The S.G.O.T. activity has been reported to be as sensitive an index of primary and metastatic cancerous involvement of the liver as the serum-alkaline-phosphatase,[14] but S.G.O.T. is unaffected by the presence of active metastatic cancer.

Surgical trauma to skeletal muscle has also been observed to result at times in increases of serum-transaminase.[15]; and the degree of muscle trauma seems to be related to the peak rise in S.G.O.T. The serum-enzyme activity cannot therefore be used as a valid index of cardiac injury in accident victims. Of neuromuscular diseases, the S.G.O.T. level is raised in progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, and dermatomyositis. Amyotrophic lateral sclerosis, progressive muscular atrophy, myæsthenia gravis, rheumatoid musculoskeletal diseases, and nerve section are not associated with increased serum-transaminase activity.

AMYLASE

With regard to plasma-amylase,[4] the evidence suggests that the activity in normal plasma is derived from various sources of which the chief are the salivary glands, the pancreas, the liver, striated muscle, adipose tissue, and fallopian tubes. The contribution of the pancreas is probably much smaller than has generally been supposed. Neither an increase in volume flow of pancreatic juice nor stimulation of pancreatic enzyme production will

8. Dalgaard, J. B. *Acta physiol. scand.* 1949, **16**, 293.
9. Tuchman, L. R., Suna, H., Carr, J. J. *J. Mt Sinai Hosp.* 1956, **23**, 277.
10. Fishman, W. H., Bonner, C. D., Homburger, F. *Proc. Amer. Ass. Cancer Res.* 1954, **1**, 14.
11. Day, E., Ying, S. H., Schwartz, M. K., Bodansky, O. *Cancer*, 1956, **9**, 222.
12. See *Lancet*, 1958, ii, 1318.
13. Wróblewski, F. *in* Hepatitis Frontiers (edited by F. W. Hartman and G. A. Logrippo; p. 447. Boston, 1957.
14. Molander, D. W. *Gastroenterology*, 1958, **34**, 1047.
15. Person, D. A., Judge, R. D. *Arch. Surg.* 1958, **77**, 892.

of itself increase serum-enzyme concentration. The important determinant is elevation of intraductal pressure. In pancreatic disease, therefore, two pathological features in the pancreas influence the height to which the amylase rises: (1) continued secretion against obstruction; and (2) the disruption of acinar cells and ductular apparatus. Because variables, including renal clearance, are involved no straightforward correlation may exist between the amylase content of any one sample of serum and the severity of acute pancreatitis; but in one series it was found that all patients with values of over 900 units did have pyrexia and pronounced leucocytosis. The rise is usually transient, often lasting only three or four days; but it has been found to persist for up to three weeks, and such persistence, when the patient is on a good therapeutic regime, indicates a complication such as abscess or pseudocyst with continuing inflammatory changes.[16] The situation is further complicated by the fact that an increase in serum-amylase level may result from administration of morphine or codeine. Rises, sometimes quite high, have also been noted in perforated peptic ulcer, not necessarily involving the pancreas, and in intestinal obstruction. A rise often follows abdominal operations, particularly for upper abdominal conditions, and rupture of an ectopic pregnancy.

OTHER SERUM ENZYMES

Other serum-enzyme determinations are of value in clinical diagnosis.[17] Glucose-6-phosphatase is very low in glycogen-storage disease and is raised in hepatitis and cirrhosis. Aldolase is diminished in progressive muscular dystrophy; it is raised after liver disease and myocardial infarction, and, fairly commonly, in cancer. Phosphohexose-isomerase is raised in progressive muscular dystrophy, after myocardial infarction, and in hæmolytic anæmia, carcinoma of the prostate, and carcinoma of the breast. Phosphoglucomutase has been shown to be raised in cancer and during hepatitis. Lactic dehydrogenase and malic dehydrogenase are both raised after myocardial infarction,[18] and the elevation tends to persist much longer than that of S.G.O.T. Lactic dehydrogenase is also raised as a result of hepatitis, muscular dystrophy, and carcinomatosis. Isocitric dehydrogenase is raised in liver disease but remains normal after cardiac infarction. Plasma-pseudocholinesterase is diminished in liver disease, whereas the true cholinesterase of the erythrocytes is much lowered in insecticide poisoning with organophosphorus compounds. Serum-cæruloplasmin is usually much diminished in hepatolenticular degeneration.

Public Health

Vaccination Against Poliomyelitis

THE Ministry of Health reports that by the end of March nearly 13,200,000 people in Great Britain had received at least two vaccinations against poliomyelitis; over 9,400,000 of them had had the course of three injections. The estimated acceptance-rate for children (1943–59 group) was 75·5% and for young adults (1933–42) 48%. The extension of vaccination to cover all persons under 40, announced by the Minister in February, has so far aroused little response.

16. Bockus, H. L., Kalsen, M. H., Roth, J. L. A., Bogoch, A. L., Stein, G. *Arch. intern. Med.* 1955, **96**, 308.
17. King, E. J. *Amer. J. Med.* 1959, **27**, 849.
18. Aquilina, J. T., Farnsworth, W. E., Short, M. L. *Amer. Heart J.* 1960, **59**, 166.

In England Now

A Running Commentary by Peripatetic Correspondents

Is there a meteorologist among our peripatetic band, circumambulating the cloisters with an occasional glance at the weather-vane or the "twelve winded sky"? Is there a weathercaster in the house? If so, will you ask him to tell us what has happened to April? A week or so ago we had her last day. She cannot come again for nearly eleven months and I don't believe she'll come then. She doesn't. This year she put her head in at the window for half a day but was gone before evening and that is about the most I've seen of her for years and years. Yet, over the centuries, she must have been pretty constant in her inconstancy. Chaucer, Shakespeare, an anonymous madrigalist who saw her "in his mistress' face", William Watson who found her girlish some sixty years ago—all took it for granted that everyone knew her endearing ways; they had only to mention her name. We all did know her; she was "just like they said", until when? Twenty years ago, or less or more? Whenever it was she just stopped coming. Her month might be cold or warm, bright or dull, possibly even wet; but the "showres sweete", the "uncertain glories", the "girlish laughter and girlish tears" were gone. In 1960 her month ended sunnily enough but with a Nor'-by-East wind that didn't let up for ten to fourteen days and the ground as dry and hard as a bone. "Pierced to the root" my foot! What is it? Melting polar ice? Electronic intoxication in the perisphere? I do hope someone can tell us. Of course what I really wanted to know is: shall I see her again and will my grandchildren ever see her at all? She was a pretty minx and good for the garden, too.

* * *

To my right in the general surgical ward lay an Italian. He had lived in this country for many years before the war, but had returned to Italy in 1939 and had fought against us. "Come over here from the Continent", said the man who was later to prove himself the curator of unreliable ward information, "to have his prostate out on the cheap." To my left was a disgruntled Anglo-Saxon who had seen better days. "But for this Welfare State nonsense I might still have the wherewithal to afford private treatment in a nursing-home." A few beds away to the left was a surgical-instrument maker. His conversation was largely about his work and his delight in it. With a grin he told me that he himself had made the instrument which the surgeon would be using to close the hole between his bowel and his bladder.

Opposite me was a retired banker who was also the author of a successful book on cookery. Closer contact with him and a description of his sufferings in and out of hospitals over the previous five years helped me to understand why, regardless of money, he chose to be in a public ward. His lively and sincere interest in the welfare of his fellow patients helped him in his own afflictions. He loathed the thought of being alone with his pain and was largely responsible for the air of cheerfulness which pervaded the ward. Alongside the banker was a bright, well-mannered boy of 15 with an undescended testicle. He informed me in confidence that he was one day going to be the Astronomer Royal. At the circumference of my immediate circle was a barrow boy—a true Cockney. I shall long remember the face of the medical student who, when apologising for his heavy-handedness in removing a dressing, was met with "Don't worry, cock; I'll 'ave yer selling nylons wiv me in the Old Kent Road when they chucks yer out of 'ere."

* * *

I remembered that a faithful attender at my follow-up clinic had bought a new car, and asked whether it was satisfactory. "Fine," he said, "But I've had to have the heater dismantled already, and it still isn't right." I sympathised. "You see, it kept splashing white spots on my trouser legs." Once more I nodded absentmindedly. "They took it out, said there was nothing wrong, and now it's hotter than ever—but it still

splashes me." Then I woke up, and as I tested his urine and found it loaded with sugar, I wondered whether car-accessory firms could use this in their advertisements: "Diagnose your Diabetes with SUDH—our Supa-Urina-Drya-Heata". No doubt they wouldn't report sugar ++, but just wotalotugot.

* * *

Entia non sunt multiplicanda præter necessitatem had been taught to us as students, when we all had thought the first four words were the ones that mattered. It wasn't for years that I learned to respect *præter necessitatem* the most. In Singapore I had seen Chinese with tuberculosis, syphilis, amœbiasis, and worms—and then realised that they hadn't come about any of them, but were brought by their relatives because they were so ill from their real complaint of, perhaps, a pharyngeal carcinoma.

I first saw Mr. X a few years ago. His eye had been removed four years previously for a retinoblastoma, and when he presented with jaundice and an enlarged liver I feared the worst; but he had infective hepatitis and recovered fully. Next time he came his wife said he had pernicious anæmia. I discounted her story, thinking that secondaries were far more likely—and to my chagrin have been treating his addisonian anæmia ever since. Last year he seemed changed. He was terribly cold, he told me in a gruff voice, and so constipated and deaf and slow that he was thinking of giving up his job. So I added thyroid extract to his medication, and all was well for the time being. Last month he came again, and I have already told you about his car-heater, and how it seemed to splash white marks on his legs. Now he has diabetes as well, you might suppose that William of Occam could keep quiet for a bit, though I suspect he is saying that the syndrome of retinoblastoma and infective hepatitis and addisonian anæmia and myxœdema and diabetes is just the entity of polygenosis, and why do I insist on multiplying it out?

* * *

If anything fills me with envy it's people who know things,
Because I haven't a memory in which I can usefully stow things;
But some people, undoubtedly closer than I to reality,
Are never at a loss to itemise and quantify actuality.
They invariably have at the tips of their tongues
Not only the surface markings of the longues
(And suchlike information, acquired long ago,
Which any medical man, save me, could reasonably be expected to know)
But the most incredible hoarded facts . . .
Such as every provision of the N.H.S. Acts,
The equations of Gaussian distribution
And where are the islands called Aleutian;
The colour-coding of electrical resistors
And which one's whom of the Mitford sistors
And all the Siberian railway gauges
And which damned year Diocletian froze wauges
And so on . . . *
It's really too depressing to go on
While, form-filling, I, recalling with effort Age, Address, and Nearest Railway Station,
Am stumped for several minutes by Year of Graduation.

But, when I consider those general-knowledgeable Joneses,
The thing that I feel, deep down in my bones, is
That largely their informational cupidity
Is explained by an underlying stupidity.
Indeed, I tell myself in a way that's smugly self-consolatory,
Intelligence and ignorance are intercompensatory
And it can't be disputed by any philosopher of whom I wot
That if, of information, you haven't a lot,
You can always scrape over life's hurdles with intelligent guesswork
(Which, in the long run, involves you in luesswork).
So I pity those poor folk who, seeking for status,
Must fill up with facts 'cause they're poor cerebratus.

* I could aye continue this diatribery
With diligent use of a reference libery.

Letters to the Editor

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—It is hard to see how anyone could possibly detract from the observations and conclusions expressed by Professor Morris—so broadly and humanely are they based.

The problem is clearly not due to a few frustrated spinsters who administer barbaric rituals, but is the outcome more probably of factors inherent in obstetric practice itself, which cause the average "normal" midwife and doctor to fail in their personal relationships with their patients.

Obstetrics appeals to many because it is a practical specialty productive of a guaranteed end-product far more tangible than the patient's gratitude. Unlike medicine and surgery, all the patients suffer from the same "disease"; they all follow the same natural history, and are subject to the same complications. Such patients tend to become units devoid of identity.

Every known obstetric hazard is expressed as a percentage. Small wonder then that a practical person working upon stereotyped material, with statistics as his master, seldom allows his imagination to wander above the fundus. The very risks which we wish to avoid are the only ones not expressed in figures. Patients who develop one-child frigidity, marital estrangements, or varying degrees of depression and fear seldom complain and never die. They simply remain "primips".

"Maternal distress" only catches the obstetrician's eye as a rising pulse-rate. Even if he does notice something overtly amiss he will not summon expert aid for two reasons. In medicine every man is his own psychiatrist. He can no more admit to a failure in human relationships than he can admit to being a bad driver. Secondly, everyone knows that most psychiatric conditions are incurable. The obstetrician, so consistently producing results, forgets that most doctors cannot hope to cure, but only to comfort their patients. None the less, when palliation is called for he sends for the radiotherapist. Why not the psychiatrist?

The midwife is subject to the monotony of normal labour without even the occasional abnormal case to leaven the dough. She resents the doctors who "pinch all the best cases", or "rush in at the last moment to pull the baby out". These feelings communicate themselves.

She forgets that the patient is not used to appearing unclothed in an undignified attitude, performing a function akin to defæcation. Endless reiteration lays calluses on her emotions. When kindness is most needed she is capable only of exhortation. Intent on five minutes' juggling at the perineum she overlooks the fact that, for the patient, this moment represents a unique end to nine months of anxious waiting.

After labour is over the midwife's task finishes where the mother's begins, and when the patient is most demanding of sympathy and explanation she is least likely to obtain it. She may even have her baby's weight kept from her to "stop her worrying". The patient's worries at this time are, in fact, like an iceberg, and it requires both imagination and insight to detect the larger submerged portion. Worse still, it takes time and patience to dissolve them. Such worries should be intelligently anticipated, not dextrously avoided.

The cure must lie with the people involved. If the obstetricians cannot accept the psychiatrists they must cultivate, as part of their equipment, the psychiatric approach. For midwives what is needed is a correct psychiatric training, the temperament to accept it, and the time to apply it.

Very little can be done about obstetrics itself. There is only one way to have a baby, and most women need help.

London, S.E.12. B. BLACKWELL.

SIR,—No-one could disagree with Professor Morris, but I noted that only once were fathers mentioned. I quote: "If a husband wants to be with his wife in labour I am certain that we have no right to deny him this experience. I actively encourage husbands to be present providing they know what to expect". What provision is there for the prenatal instruction of expectant fathers? I am convinced that the husband's influence is very important and that he, rather than obstetrician or nursing staff, determines a woman's attitude to pregnancy and childbirth. Mere attendance at the birth is not enough and in too many cases the wish to attend is engendered by curiosity rather than a desire to participate.

It should be possible for the obstetrician to have at least one interview with each expectant father and to organise a short series of lectures, illustrated by colour films, to give the necessary instruction. It would be a chance to help those men who, by their ignorance or ineptitude, cause their wives avoidable anxiety. In the first stage of labour the husband could keep his wife company and minister to her minor needs. More personal contact with the fathers would give both obstetricians and nursing staff a better understanding of both mother and infant. Hospitals could then, in this respect, compare more favourably with domiciliary midwifery.

Preston. NORA WILKINSON.

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—We were interested to read the article of Feb. 6 by Professor McMichael and his colleagues on the excretion of ^{14}C-labelled bretylium tosylate, the hypotensive drug first described in your columns by Boura et al.[1] in 1959. Our experience of a six-month follow-up of 25 patients treated with bretylium for six months has been similar to Professor McMichael's. A good control of blood-pressure was obtained in 19 patients, moderate control in 4 patients, and renal failure developed in 2 patients while on therapy. It was found that tolerance to bretylium gradually developed in 15 patients, and an initial dose of bretylium 200 mg. three times a day was increased after some weeks in some instances to 800 mg. or more three times a day. In one patient a total daily dose of 3200 mg. was inadequate to control the hypertension. Chlorothiazide was useful as an additional drug and allowed the dosage of bretylium to be reduced.

We found that bretylium was an effective hypotensive agent and reached maximum effect in between three and six hours. The side-effects were not prominent although 14 out of 25 in the series complained of a transient stuffiness of the nose. 5 patients had rather loose motions and 4 a transient frequency of micturition. Bretylium affected the mental state and appeared to have a tranquillising effect, althought in 2 patients the reverse occurred and severe psychotic manifestations developed shortly after initiation of bretylium treatment. All patients on previous therapy found a great relief from the severe dryness of the mouth, constipation, and blurring of vision. A typical remark was "it's nice to be able to see again". Impotence was a complaint in 1 male patient.

However, sudden hypotension of moderate severity was a feature in 5 patients and may have been due to irregular absorption of the drug. 2 patients with renal failure were found difficult to stabilise and in one patient 300 mg. of bretylium daily was sufficient to produce severe hypotension. The 1 death in this series was due to progressive renal failure.

The six months' trial of bretylium in 25 hypertensives has established satisfactory control in most cases, but sudden hypotension is a real difficulty and further study in patients with renal impairment is indicated. This clinical observation is in accord with the low excretion of ^{14}C-labelled bretylium in renal failure observed by Professor McMichael's team at Hammersmith.

It is therefore urged that caution should be advised in the use of bretylium particularly where there is renal insufficiency.

St. Helen Hospital, Barnsley. I. MCLEAN BAIRD
I. UL-HAQ.

1. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *Lancet*, 1959, ii, 17.

THE HÆMATOLOGICAL CHANGES IN PARABIOSIS INTOXICATION

SIR,—In a preliminary communication (March 26) Dr. Gurney and Dr. Taylor state: "We here report the development in parabiosed homologous mice of a condition resembling that known as the parabiotic intoxication syndrome of rats". In recognition of the numerous investigators who have studied the response in that animal, the condition described would be more properly designated as identical with the parabiosis intoxication syndrome of mice, rather than similar to that which occurs in rats. Precisely what is meant by the term "homologous mice" is uncertain, for the C3H and AKR strains are not genetically homogeneous.

Studies on parabiotic rats have led us to formulate the hypothesis that the anæmia which occurs in one member of an intoxicated pair and the polycythæmia of its twin are due to a shift of blood from one to the other.[1–3] Gurney and Taylor believe their findings to be incompatible with this thesis although they present neither adequate reasons for this conclusion nor an alternative explanation. The data which they present, however, merely confirm those obtained by many other investigators who have studied murine parabiosis intoxication, and were utilised by us in deriving a theory to explain the mechanism of the disorder.

In the mouse it has been reported that parabiotic compatibility requires the presence of identical alleles at the H-2 locus. Thus when a pure mouse is joined to a hybrid derived from crossing the pure strain with another, parabiosis intoxication inevitably ensues and it is the hybrid which becomes anæmic.[4]

Further experiments in the mouse have led Eichwald,[5] using criteria quite different from those which in rat studies led us to infer that the hæmatological changes were due to unequal blood transfer, to the same conclusion.

In summary the findings are that the anæmia is due neither to hæmolysis nor to depressed erythropoiesis, and the polycythæmia of the twin cannot be ascribed to increased erythropoiesis. Neither of these states can be produced in recipient hybrids or pure single animals by repeated injections of blood, spleen, or lymph-node suspensions from a donor of the opposite genetic constitution, even though donors and recipients of differing genotype develop intoxication when joined. The combined red-cell mass of pairs remains constant, and when intoxication develops or temporarily reverses, the increased red-cell mass in one partner is balanced by an equal decrease in the twin. Eichwald concludes: "The data obtained suggest that the symptoms of intoxication are due to a massive shift of red cells from the intoxicated mouse to its partner."

1. Hall, C. E., Hall, O. *J. exp. Med.* 1956, **103**, 263.
2. Hall, C. E., Hall, O. *Amer. J. Physiol.* 1956, **184**, 155.
3. Hall, C. E., Levin, W. C., Hall, O. *Proc. Soc. exp. Biol., N.Y.* 1957, **96**, 780.
4. Eichwald, E. J., Lustgraaf, E. C., Strainer, M. *J. nat. Cancer Inst.* 1959, **23**, 1193.
5. Eichwald, E. J., Lustgraaf, E. C., Fuson, R. B., Pfaff, J. P., Jr. 4th Tissue Homotransplantation Conference, *Ann. N.Y. Acad. Sci.* 1960 (in the press).

In the absence of adequate evidence to the contrary, we believe this to be the explanation which best fits the available facts.

University of Texas,
Galveston, Texas.

CHARLES E. HALL
OCTAVIA HALL.

ADDICTION TO DRUGS

SIR,—It is true that in the United Kingdom an addict may apply to any qualified doctor for a supply of drug but it is entirely inaccurate for Mr. Harney to state (May 7) that " we have no opiate problem here because narcotics are freely dispensed by doctors to all askers ".

The only " magic alchemy for the control of narcotic addiction " which we possess consists of the regular inspection of all chemists', doctors', dentists', and veterinary surgeons' dangerous-drugs registers, and the fact that drug addicts are treated as patients.

In America the addict is regarded as a criminal and as such he avoids treatment and supervision. Because the drug can only be obtained there illicitly the price is exorbitant and addicts become traffickers in order to pay for their own supply.

In this country drugs are available to the bona-fide addict under the National Health Service provided that there is a satisfactory indication for prescribing them and so long as the patient undertakes to accept treatment of his addiction.

Accordingly, there is no equivalent temptation here for an addict to sell some of his drug or endeavour to create addiction in others so as to develop a source of income for his own purchases.

America will continue to have a serious drug problem so long as addiction is equated with crime, for criminal vested interests will ensure that there is an increasing number of addicts to swell the fantastic profits derived from the peddling of narcotics.

The emphasis must be shifted from punishment to treatment, and the latter should be made available free of charge and without penalties to all addicts.

ELLIS STUNGO
Honorary Secretary,
Society for the Study of Addiction.

London, W.1.

FLUORIDATION

SIR,—Mr. Capstick (April 16) implies that the physical suffering and expense attendant upon dental caries is insignificant, and can easily be overcome by fitting everyone with dentures. Such a view is indefensible.

The report of the Ministry of Health for 1958, part 1, states that the amount of fees authorised by the Dental Estimates Board for 1958 for payment to dentists was £44 million, and that 2,352,000 courses of dental treatment were given to children. Nearly ten million teeth were extracted, of which two million were removed under general anæsthetic. Much of this misery and expense could be saved by the simple and safe procedure of adding fluoride to the community water-supply.

In the Ministry of Health reference note, no. 9, of July, 1955, it is stated categorically that there is no scientific evidence whatever that fluoride at a level of 1 part per million has any deleterious effect on the health of adults or children. For example, in a community whose water-supply contained as much as 8 parts per million of fluoride, careful examination was made of a group who had consumed this water for a minimum of 25 years, and showed that, apart from mottling of the teeth, no important effect could be found in these people to differentiate them from those in a similar community with a low fluoride content in its water.

Very many careful and scientific surveys of a similar nature can be quoted. It can be accepted that in the present state of knowledge, fluoridation is absolutely known to be safe; very much safer, for instance, than dental extraction under general anæsthesia.

The Central Council for
Health Education, London, W.C.1. A. J. DALZELL-WARD.

THE CARPAL-TUNNEL SYNDROME

SIR,—The correspondence on this syndrome, ending with the interesting views of Mrs. Draspa (April 9) on the psychological aspect, point to a multiple pathology for this condition.

I have seen several antenatal patients who, in the later stages of pregnancy, had symptoms and signs of this syndrome. Some of these patients had toxæmia of pregnancy, with œdema of the fingers and wrists. Treatment with hydrochlorothiazide to control the œdema reduced or resolved the symptoms in some patients. The condition always subsided after labour and therefore no long-term treatment was required. These cases support the idea of nerve compression by tissue œdema at the wrist.

Netley Abbey,
Hampshire. B. J. FOSTER.

THE NATURE OF HYPERTENSION

SIR,—In the discussion of the nature of essential hypertension, Dr. Morrison and Professor Morris [1] used the systolic blood-pressure distribution curves to analyse " bimodality ". We cannot accept their conclusions because we consider that systolic blood-pressure alone cannot be used as a quantitative method to study essential hypertension.

It has been clearly established that the systolic pressure is influenced directly by (1) conditions which increase the stroke-volume of the left ventricle, and (2) conditions which increase the rigidity of the aorta. As many factors can influence these conditions, the range of variability of systolic pressure is so great, that casual readings can easily be shifted by chance very far from the true mean figures. This fact hampers work with systolic figures in clinical investigation, and we do not use systolic scores to analyse results in our treatment of hypertension.

The diastolic blood-pressure is the true measure of the arteriolar peripheral resistance—the essential key in the development of hypertension. The severity of hypertension is determined by this diastolic pressure.[2 3]

According to Morrison and Morris, their diastolic pressure levels were distributed " continuously ", without bimodality. The bimodality appears only in the systolic curves. As the systolic curve does not truly represent the distribution of blood-pressure in the general population, we can accept only the existence of the unimodality of the diastolic curve.

Aguirre Hospital,
University of Chile School of Medicine,
Santiago, Chile. R. CRUZ-COKE.

PLASMODIUM MALARIÆ IN " NEPHROTIC SYNDROME "

SIR,—I found the preliminary communication by Dr. Gilles and Dr. Hendrickse (April 9) about a relationship between the nephrotic syndrome and infection with *Plasmodium malariæ* in Nigerian children of particular interest because their pædiatric experience in Ibadan, Nigeria, sharply contrasts with mine in Freetown, Sierra Leone.

Their report is based on 48 new cases attending University College Hospital over a period of less than one year. In the children's medical ward at Connaught Hospital, Freetown, during the period November, 1955, to September, 1959, I can remember seeing only 3 cases of the nephrotic syndrome in children under 10 years old. Malarial parasites, other than *P. falciparum*, were virtually non-existent in the Freetown area. During the six months from March to August, 1959, of a total of 422 admissions to the children's ward, there were 54 proven cases of malaria, all reported as being *P. falciparum* infections.

1. Morrison, S. L., Morris, J. N. *Lancet*, 1959, ii, 864.
2. Perera, G. A., Brust, A. A., Wilkins, R. W. *J. Amer. med. Ass.* 1958, **166**, 648.
3. Cruz-Coke, R. *Rev. med. Chile*, 1958, **86**, 438; *Lancet*, 1958, ii, 216.

The virtual absence of *P. malariæ* and the nephrotic syndrome in Freetown tends to support the theory of the ætiological role of *P. malariæ* in the nephrotic syndrome, particularly as the two West African territories of Nigeria and Sierra Leone have so many pædiatric problems in common.

Queen Elizabeth Hospital, Aden. F. STEPHEN CARTER.

THE SHORTAGE OF NURSES

SIR,—I would strongly support Mr. Malkin's appeal (April 30) for an urgent approach to the problem of the serious shortage of nurses in our hospitals. He suggests a central body consisting of representatives of the Ministry of Health, the hospitals themselves, the British Medical Association, and the Royal College of Nursing to be formed to tackle this problem. I agree that this is a sound, long-term view but the problem is too acute for this approach.

While agreeing that there are other factors in addition to the question of salary, I am convinced that the root cause of our present troubles is our false sense of values in relation to the hopelessly inadequate remuneration of hospital sisters. Mr. Malkin quotes the "Alice in Wonderland" example of a hospital sister receiving less salary than a ward orderly may receive with overtime. Anyone familiar with hospital routine will know that experienced hospital sisters are extremely valuable members of the medical profession and are really the equivalent of specialists in nursing, as far as the treatment of patients is concerned. They should, therefore, be paid for their services. They deserve a salary which would allow them to run a car and enjoy other amenities which are worthy of the privileged, responsible posts they hold.

At present the maximum salary of a hospital sister after 7 years of service is £820 p.a. After all deductions she receives less than £30 per month. I see no reason why a senior sister should not be paid at least £1200 p.a. If this were done there would be a genuine worthwhile incentive for suitable candidates to take up nursing as a career.

Halifax. GEOFFREY HYMAN.

REDUNDANT ALPHABETS

SIR,—We have almost lost sight of Shaw's alphabet in the issues (and dubious arguments) of redundancy. G. B. S. would not have objected: he himself often started fights on the touch-line to bring spectators to his game. But Dr. Thomas' last fight (May 14) was so skilful and logical as far as it went that it might draw attention away from the game.

His distinction between noise and redundancy was very well made. The choice of the word "noise" was not particularly happy, but his meaning is clear and no-one would doubt his conclusion that noise is noxious and redundancy potentially protective. Following this up, he points out clearly that redundant letters make a word more specific and therefore less easily confused with other words. What happens if we follow this argument to its logical conclusion? The most specific words, and therefore the least ambiguous, would be ideograms, but it is a commonplace that ideographic scripts are accompanied by the highest illiteracy. Why is this? There must be some factor other than ambiguity which supports illiteracy. Quite simply, it is the total number of sound-signs which have to be learned. It may be quite true to say that two highly redundant ideograms cannot be visually confused, but what is the good of that if the meaning of neither is known? Redundancy will certainly protect against errors in transmission but if the signals are not understood there will be no transmission as far as the reader is concerned.

It was not lack of redundancy in the script which made it so difficult for 4th-century Japanese to learn to read and write. It was having to memorise 40,000 distinct characters. In the 8th and 9th centuries the kana syllabary of 48 was introduced, and nowadays more and more is written in the Roman alphabet. All over the world when scripts have evolved it has always been in this direction from a highly redundant non-phonetic one to a less redundant phonetic script. This was my meaning, though badly put, when I said that occasionally to use the letters "ugh" for the sound "f" as in the word "cough" did not protect against errors in transmission. I should have said that such usage might result in nothing being transmitted at all.

If future generations forget that "cough" was pronounced "cof" I am afraid that Dr. Thomas' jingle is going to fall pretty flat. But given a Mandarin who remembers the usage, the joke is most likely to survive the sabotage of posterity's careless type-setters if you write:

It wasn't the cough that carried him ough,
But the coughin they carried him ough in.

Lee-on-Solent, Hants. A. S. JARRETT.

MERIT AWARDS

SIR,—There is much discussion regarding merit awards to practitioners under the N.H.S. and how this money (£500,000) should be allocated. It seems to me this sum should be awarded to private practitioners who for good reasons could not enter the Service and whose livelihood has been seriously curtailed by the N.H.S. The practices of those joining the Service were purchased by the Ministry, but no consideration was given for the harm done to private doctors. I say in justice and fairness this sum should be given in compensation to them. If legislation is necessary, let Parliament legislate.

London, W.1. M. W. BROWDY.

SIR,—Would you permit me a hollow laugh? If 13% available to anæsthetists is contemptuous, is not the proposed 3% to general practitioners insulting?

Writtle, Essex. J. TUDOR PEMBLETON.

INTERMITTENT POSITIVE-PRESSURE RESPIRATION IN INTRACTABLE STATUS ASTHMATICUS

SIR,—May I thank Dr. Buzzard (May 7) for his constructive criticism and reply to his important points about sedation in status asthmaticus?

The three fatal cases mentioned in my paper of April 23 received, respectively: no sedation; 5 ml. paraldehyde and 150 mg. amylobarbitone; chlorpromazine 50 mg. and promethazine 50 mg. p.r.n. q.6h. To the remaining seven (unreported) patients admitted to the Salisbury General Infirmary with status asthmaticus in 1959, high doses of sedatives were often given. Three patients had chlorpromazine 50 mg. and promethazine 50 mg. q.6h. from three to five days; another patient received 100 mg. each of chlorpromazine, promethazine, and pethidine four times within twenty-four hours of admission.

Two patients did not need sedation. In one patient, admitted in severe distress with marked cyanosis and able only to talk in gasps, the exhibition of chlorpromazine 25 mg. and promethazine 25 mg. coincided with circulatory collapse and an absent radial pulse. This collapse was relieved by the intravenous injection of 3 ml. 1-in-1000 adrenaline over four minutes.

Ten of the total of twelve patients with status asthmaticus mentioned social or emotional problems on admission, and three of these patients, one of whom subsequently died, were referred for a psychiatric opinion.

Sedation is an integral part of the orthodox management of status asthmaticus (M.R.C. Trials Subcommittee [1]).

The first fatal case of bronchial asthma to appear in the literature [2] was a female morphine addict aged forty, who

1. *Lancet*, 1956, i, 803.
2. van Leyden, E. *Dtsch. militärärztl. Z.* 1886, **15**, 51.

lived long enough to die from congestive cardiac failure induced by her final attack of status asthmaticus.

While it is admitted that excessive sedation may be deleterious in status asthmaticus, it is submitted that liminal sedation is often beneficial and will neither accelerate nor alleviate progressive bronchial occlusion.

Atkinson Morley's Hospital,
Wimbledon, London, S.W.20. BRYAN BROOM.

THE PERSONAL DOCTOR

SIR,—Before this instructive correspondence closes I should like to ask Dr. Fox how much his definition of a personal doctor differs from that which I was rash enough, three years ago, to suggest for a general practitioner: "A doctor in direct touch with patients, who accepts continuing responsibility for providing or arranging their general medical care, which includes the prevention and treatment of any illness or injury affecting the mind or any part of the body".[1] Analysis of significant differences between the two definitions should help this discussion.

In our country the doctor we now recognise as a good general practitioner is part of a comprehensive medical service in which he plays an important role—bringing the resources of modern medicine to the homes and bedsides of his patients; supporting, comforting, and befriending them and their families in the same personal way he has done in the past; and advising and guiding them wisely when they need to seek specialist help.

That general practice is evolving like this, fitting into the modern framework of medicine, is natural. It is a challenge to us all to improve this branch of our profession in the ways which Dr. Fox suggests, but *not* a reason for changing its name.

London, S.W.1. JOHN H. HUNT.

*** Dr. Fox writes: "My article was a plea for the preservation and strengthening of the independent practitioner as Dr. Hunt describes him. But I argued that his days are numbered unless he is seen to justify his independence. Whether we give him a new name is unimportant, for names notoriously outlast functions. But in judging his adequacy and survival-value we should apply, I suggested, a new criterion. Is he giving better personal care than would be obtainable from a hospital group?"—ED. L.

PHOTOCOPYING

SIR,—I have read with interest the letter from Dr. Graham in your issue of May 14, and I would subscribe fully to his condemnation of the use of trichlorethylene and of tricresyl phosphate when used in transparentising solutions for application to opaque originals which are to be reproduced by contact printing. But I think Dr. Graham has assumed the existence of a danger which does not exist or is very remote. Over nearly forty years' connection with the photoprinting industry I have not known trichlorethylene or tricresyl phosphate to be used in transparentising fluids.

Further, it should be borne in mind that transparentising is not a regular procedure in the photoprinting industry. It is an application made when original drawings have become so old through age or handling that it is desirable to make them more transparent before copying, and as such the individual is exposed neither to the effects of a high toxic concentration of the vapours of the solvents used, nor to the long-continued influence of a low vapour concentration whereby a cumulative physiological effect is produced in the system.

1. *Brit. med. J.* 1957, i, 1075.

Another substance which Dr. Graham mentions, namely carbon tetrachloride, although banned in industry except under controlled conditions of ventilation, has for many years been freely sold for purposes of dry-cleaning in the household.

The point I would make is that the transparentising of prints is not an operation often encountered in the photoprinting industry, which is in no way dependent upon the general usage of the solvents to which Dr. Graham quite rightly takes exception.

H. D. MURRAY
Loughton, Essex. Director, Ozalid Company Limited.

PERIORBITAL ŒDEMA AFTER EXERTION

SIR,—Sometimes the cases that Captain Mullan refers to (April 9) have predominant œdema of the conjunctiva and lids, the lids less frequently. It is a white chemosis, which subsides spontaneously but more rapidly when a corticosteroid is applied locally.

It may be due to an allergy to lactic acid. Loose tissues such as the conjunctiva and lids seem to be extremely sensitive to lactic acid allergy. We suggest hydrocortisone-eye drops instilled before the exertion. A skin-test may be able to confirm the diagnosis.

Academisch Ziekenhuis,
Ghent, Belgium. ADOLPH NEETENS.

METAHEXAMIDE IN THE TREATMENT OF DIABETES MELLITUS

SIR,—Metahexamide [1-(3-amino-*p*-tolylsulphonyl)-3-cyclohexylurea], a new oral hypoglycæmic agent, was recently introduced for the treatment of diabetes mellitus and has since been withdrawn owing to its toxic effects on the liver.[1 2] Its half-life is 18·2 hours [3] as compared with 35 hours for chlorpropamide, 40 hours for carbutamide, and 3·5 hours for tolbutamide.[4]

The drug was given to 27 diabetic patients as a single daily dose before breakfast, 300 mg. on the first day, 200 mg. on the second day, and 100 mg. on subsequent days. All patients were treated for at least seven days before the compound was considered to have failed to control their diabetes. A patient was considered to be well controlled on metahexamide when the morning specimen of urine was sugar free and a blood-sugar at least $1^1/_2$ hours after breakfast below 210 mg. per 100 ml.

The first group of 16 patients consisted of 9 who had failed to respond to tolbutamide, 1 who had failed to respond to chlorpropamide, and 6 who had failed on both tolbutamide and chlorpropamide, on separate occasions. None of these 16 cases responded to metahexamide. All were the type of case which would be expected to respond to oral hypoglycæmic agents.[5 6] A further 11 cases were changed from good control on tolbutamide, chlorpropamide, or insulin, and 9 of these showed good control on metahexamide. Of the 2 cases which failed, 1 had previously been well controlled on chlorpropamide and the other was an obese diabetic who has since been shown to be unresponsive to other oral hypoglycæmic agents.

The weight remained unchanged in 14 of the 27 cases treated; 8 patients lost weight and in 6 cases there was a relapse in the diabetic control: 5 patients gained weight and of these only 2 showed a satisfactory response to metahexamide. No toxic effects were recorded in any patient in our series.

There is sufficient evidence in this small series to show that metahexamide has no advantage over tolbutamide and also has a smaller range of activity than chlorpropamide.[7] The trial was stopped at this stage following a report that metahexamide had produced necrosis of the

1. Owen, J. A. *Metabolism*, 1959, **8**, 667.
2. Mach, B., Field, R. A., Taft, E. B. *New Engl. J. Med.* 1959, **261**, 438.
3. Morgenstern, L. L., Garrett, E. R. *Ann. N.Y. Acad. Sci.* 1959, **82**, 502.
4. Stowers, J. M., Constable, L. W., Hunter, R. B. 1959, *ibid.* **74**, 689.
5. Nabarro, J. D. H. *Brit. med. J.* 1959, i, 1466.
6. Oakley, W. G. *Practitioner*, 1959, **183**, 478.
7. Jackson, D., Oakley, W. G. *Lancet*, 1959, ii, 752.

liver in 1 case. There would therefore seem to be no indication for the use of metahexamide in the treatment of diabetes, and it has now been withdrawn by the manufacturers.

Diabetic Clinic, King's College Hospital, London, S.E.5.

DERRICK JACKSON
WILFRID OAKLEY.

SALMONELLA OSTEITIS

SIR,—Dr. Reid's comments (April 9) on the possible ætiological role of *Salmonella enteritidis* var. *chaco* in some of our cases of salmonella osteitis [1] were much appreciated. We must point out however that none of our cases in which *S. enteritidis* was isolated resembled the syndrome described by Cosgrove and Reid,[2] nor was the clinical picture presented by these cases essentially different from that presented by cases in which other strains of salmonellæ were isolated. In all our patients pain and swelling over the affected bones were *presenting* symptoms, and not sequels to a typhoid-like illness. Finally, it was confirmed bacteriologically that we were dealing with *S. enteritidis* var. *jena*.

Children's Department and Department of Bacteriology, University College Hospital, Ibadan, Nigeria.

R. G. HENDRICKSE
PATRICK COLLARD.

POSTURAL TREATMENT OF ADHESIVE OBSTRUCTION OF BOWEL

SIR,—Since decompression via an intestinal tube can at times relieve this form of obstruction it is plain that in such instances there is no permanent stricture. If instead a laparotomy is done one can sometimes lift the laden bowel on the proximal side of the kink into alignment with that on the distal side. It should be possible to use gravity for this unkinking, and in selected patients posturing has been found effective. On such occasions the patient is spared the discomfort of intestinal tube and operation.

Postures used.—The history may indicate a posture. If not I use the following sequence. With the foot of the bed elevated on 18-in. blocks, the patient lies (i) on his right then (ii) on his left side and then (iii) prone. Twenty minutes are spent in each position. If all fail the patient is put in (iv) the upside down position. Here he takes his weight on his shoulders, the trunk and lower limbs resting against the wall.

It is appreciated that the diagnosis is not fully confirmed unless the adhesion is seen at operation and that the examples which follow are open to objection on this score but one object of the method is to prevent operation.

(1) In October, 1954, Mrs. A had an operation for bilateral pyosalpinx. Nine days later, a gynæcologist, Mr. H. R. Thomson, and I operated for intestinal obstruction. Several inches of small bowel were densely adherent to the pelvic floor. In March, 1955, she was readmitted with a second obstruction and treated by intestinal tube and intravenous fluid. On Oct. 31, 1955, the patient had an exactly similar midline hypogastric colic. Two minutes after being placed upside down she felt a gurgling and had immediate relief.

(2) Mr. B was admitted to Launceston General Hospital in 1955 after thirty-six hours of upper median abdominal colic and two vomits. In 1940 he had an appendicectomy, and in 1947, 1951, and 1954 laparotomies to divide adhesions. At the 1955 admission postural treatment was given. With the foot of the bed raised, the right lateral position was soon followed by passage of wind per rectum and relief of pain.

(3) Mrs. C was admitted to Launceston General Hospital in August, 1958, with a five-hour history of hypogastric colic and six vomits. She had an appendicectomy in 1942 and pelvic cellulitis in 1946. Radiography of the supine abdomen showed two gas-filled coils of small bowel and, in the erect position, fluid levels. Postural treatment was given and in the first three positions the patient vomited. Her body was then supported against the wall while she took her weight on her shoulders. Soon she felt a rumble which ended in the passage of flatus and relief of pain.

Selection and safeguards.—(1) Posturing should never be attempted if (*a*) a closed loop of small bowel or (*b*) a large bowel obstruction is likely, the latter because the ileocæcal valve may remain competent thus virtually converting the obstructed colon into a closed loop. (2) Temporary disimpaction of a mobile object at a neoplasm might conceivably follow posturing. Accordingly at times I have sought tumours after postural treatment, so far with no result. (3) In a patient referred by Dr. R. A. Godfrey-Smith posturing failed. Intubation then also failed. Operation revealed a hard band causing pressure necrosis of bowel wall. This illustrates the well-known need for very early operation if conservative measures fail. Provided this danger is remembered I believe that posturing will upon occasion obviate intestinal tube and/or operation in adhesive obstruction.

I have not seen this idea in print: it is the result of a question put in 1950 by Mr. C. Craig. On dividing a fibrotic and obviously matured adhesion he asked how it was that the patient had avoided intestinal obstruction for so long.

Launceston, Tasmania.

W. W. WOODWARD.

EXPIRED-AIR RESUSCITATION

SIR,—Dr. Gardner (May 7) mentions that it is no great hazard if air is blown into the stomach. Though the most important thing, of course, is that oxygen quickly reaches the patient's lung, blowing air into the stomach during inflation of the lung is most undesirable: not so much because it may impair diaphragmatic movement, but because it may provoke dangerous regurgitation. It is often reported that the use of expired-air insufflation resulted in water and stomach contents being forcefully expelled from the victim. Sometimes stomach contents have been blown into the deeper airways of the patient, thereby jeopardising what seemed to be an otherwise successful resuscitation. It may also be unwise, therefore, to express air from the stomach, for this may result in stomach contents being expelled too.

Probably when the air-passage is clear and the inflation pressure is limited to 20 cm. water, then air is rarely blown into the stomach. But it is hardly possible to teach this, and even more to have a "frightened" lay rescuer remember limiting inflation pressure. A practical possibility, however, seems to be inflation through the nose rather than the mouth. In studies [1] with more than 1000 anæsthetised, curarised, and non-relaxed patients, it was found that inflation through the nose seldom resulted in only stomach inflation, possibly because this route with its increased resistance cuts down the peak pressure reaching the pharynx. Incidentally, not a single case of nasal obstruction was observed during this study.

That practice manikins "form an integral part in any comprehensive training scheme" seems true.[2 3] However, it must be presumed that, apart from being suitable for the actual training technique, the manikin is not by itself a source of spread of infection. It would be silly to have hygienic objections with expired-air resuscitation in an emergency and not safeguard against cross-infection during training. Not only the exterior of the manikin's face must be capable of disinfection, but also its air-passages, including its lung (and stomach).

Dr. Gardner says "the impossible—practice manikins—

1. Hendrickse, R. G., Collard, P. *Lancet*, Jan. 9, 1960, p. 80.
2. Cosgrove, P. C., Reid, J. D. *Trans. R. Soc. trop. Med. Hyg.* 1955, **47**, 153.

1. Elam, J. O., Greene, D. G., Schneider, M. A., Ruben, H. M., Gordon, A. S., Hustead, R. F., Benson, D. W., Clements, J. A. *J. Amer. med. Ass.* 1960, **172**, 812.
2. Ruben, A., Elam, J. O., Ruben, H. *Lancet*, 1959, ii, 69.
3. Ruben, H., Ruben, A., Elam, J. O., Benveniste, D. *Ugeskr. Læg.* 1960, **122**, 215.

will take a little longer". A practice manikin is now constructed to fulfil not only the technical demands (inflation through nose or mouth; mimicking air-passage obstruction and its release; stomach inflation when improper inflation pressure is used), but also allowing proper hygienic precautions to be taken [4]; and such a manikin is available in Denmark (Testa Laboratorium, Copenhagen).

Department of Anæsthesia,
The Finsen Institute, Copenhagen. HENNING RUBEN
Director.

SIR,—There are a number of points on which I should like to comment. First, patients whose breathing has stopped or is failing may be classified into three groups:

(*a*) Those who will recover with or without treatment.
(*b*) Those who require assistance in respiration in order to survive.
(*c*) Those who are beyond aid.

Artificial respiration is taught for the benefit of the second group, but since this is not homogeneous the extent of the help which is needed will vary from complete dependence on the method employed to a short application of such a manœuvre. Testing these procedures is therefore difficult in the " field ", and for a realistic assessment the measurement of tidal volumes and oxygen uptakes on paralysed but otherwise normal subjects must be used instead. In this way a number of important factors are ignored, such as the effect on the cardiovascular system, but such an appraisal does give the Holger-Nielsen method a good deal of support in preference to other manual procedures.[5] Further, it is effective in patients whose lungs are resistant to deformation, as in emphysema, and this may be of importance under the conditions where artificial respiration may have to be employed.

On the other hand, expired-air resuscitation seems to have had little testing on the edentulous subject and in patients with a decreased lung compliance (as in emphysema), both of which would place the operator and the patient at a disadvantage. The fact that an airway may not always be available is an argument against the procedure, as is the need for apparatus in Eve's method. In addition, the anæsthetist is not the man who is going to do artificial respiration in most cases out of hospital. The layman who is going to carry it out must be trained and the technique which he is taught must be effective, simple, and in no circumstances harmful.

The "mouth-to-mouth " technique is difficult to perform efficiently and at present its value is unproven in conditions other than the ideal. But reports on the Holger-Nielsen procedure [6 7] led the medical advisers of the St. John Ambulance Association, the British Red Cross Society, and the Royal Humane Society, amongst others, to recommend its adoption. Surely it is unwise to change the standard teaching until the evidence is more conclusive.

University of Bristol. R. ST. J. BUXTON.

TREATMENT OF DEAF CHILDREN

SIR,—A number of our profession have been approached by medical practitioners concerning the rehabilitation of children suffering from adventitious deafness. We should be grateful if, through your columns, we might stress the urgency of such treatment to conserve their communication skills, which, without immediate treatment, are speedily lost.

This society will be glad to supply the names of qualified specialist teachers of the deaf who could be called upon to deal with this problem in any given locality.

2, Newcourt Road,
Charlton Kings,
Cheltenham, Glos. J. DIMOND-HOGG
Honorary secretary,
Society of Teachers of the Deaf.

4. Ruben, H. *Brit. med. J.* (in the press).
5. Buxton, R. St. J., Kazantzis, G. *Med. Pr.* 1956, **236**, 611.
6. Holstein-Rathlou, E. von. The Holger-Nielsen methods: history and scientific basis. Copenhagen, 1950.
7. Gordon, A. S., Affeldt, J. E., Sadove, M., Raymon, F., Whittenberger, J. L., Ivy, A. C. *J. appl. Physiol.* 1951, **4**, 408.

NON-STERILE INJECTIONS?

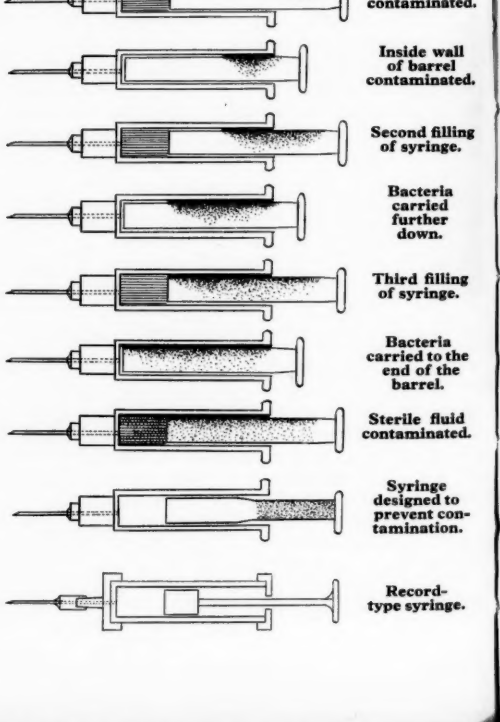
SIR,—I believe that it is not generally appreciated that contamination of an injection fluid by other than blood-borne organisms can occur, when using a single all-glass syringe for a series of immunising injections, unless strict attention is paid to the method of manipulation.

A commonly used technique seems to be to hold the ampoule or the multiple-dose bottle, in one hand, placing the index finger of the other hand on the end of the barrel of the syringe and in contact with the shaft of the piston (see figure), and exerting traction with the middle finger and the thumb. While this is a perfectly suitable technique for a single injection with an all-glass syringe, or even for a series of injections with a Record-type syringe, it should never be used for a series of injections with an all-glass syringe. The bacteria which are deposited on the piston by the finger are carried down during injection of the fluid, to come into contact with the inside wall of the barrel of the syringe. With the next filling of the syringe the sterile fluid washes the contaminated inside wall of the barrel.

It might appear, at first, that this contamination cannot occur when only small volumes of fluid are taken into the syringe, and the piston is not withdrawn to its fullest extent; but a few moments' reflection will reveal the fact that contamination by the fingers of the proximal end of the shaft of the piston, will result in contamination of the whole of the inside wall of the body of the syringe after two or three repeated withdrawals and ejections—the bacteria are carried further down inside the syringe with each successive movement of the piston (see figure). It is even possible that the process may be hastened by currents set up as a result of pressure changes within the syringe.

Contamination of a sterile fluid within the syringe itself can occur, in a like manner, if the above technique is used for withdrawing the piston of an all-glass syringe before the introduction of air into a multiple-dose bottle. It may well be that the sterile fluid comes into contact with the contaminated inside wall of the syringe with the very first filling.

In order to avoid contamination of the piston of an all-glass syringe, a technique must be practised whereby the ampoule or the bottle, and the barrel of the syringe are both held in the


Piston contaminated.
Inside wall of barrel contaminated.
Second filling of syringe.
Bacteria carried further down.
Third filling of syringe.
Bacteria carried to the end of the barrel.
Sterile fluid contaminated.
Syringe designed to prevent contamination.
Record-type syringe.

fingers of one hand, leaving the other hand free to pull on the piston by touching the "handle" part only. Even then, with the piston fully withdrawn, strict vigilance is necessary during subsequent manipulation, in order to avoid touching the exposed shaft with the fingers or with the palm of the hand.

The provision of a freshly sterilised syringe and needle for each injection at immunisation clinics must surely be the safest and most sensible technique to adopt. However, when circumstances are such that one syringe only is to be used for a series of immunising injections, I would suggest that the Record-type syringe should be the syringe of choice. Contamination of the piston of the Record syringe by the fingers or by the hand cannot occur, and no special technique or vigilance is necessary (see figure).

For those who prefer an all-glass syringe on all occasions, possibly the manufacturers would be able to produce a syringe with a piston so designed that it made contact with the inside wall of the barrel for a part of its length only, the rest of the glass shaft being of slightly smaller diameter (see figure). The use of such a syringe would eliminate, in a like manner, any possibility of accidental contamination of the piston and of the syringe contents.

Nelson, New Zealand. JOHN MEAD.

A PILLOW FOR USE IN CERVICAL MANIPULATION

SIR,—When working single-handed in general practice one often has difficulty in applying counter-traction during manipulations of the neck. In order to obviate this a pillow has been designed and its method of use is illustrated below.

The pillow is triangular in cross-section, being approximately 7 in. from base to apex and 20 in. each way at the base. I use a couch 6 ft. 6 in. long, 20 in. wide, and 20 in. high for

manipulations (the same couch can be used for ordinary examinations). The pillow is placed at the end of the couch (see figure) and the patient's shoulders are brought up to the apex thus leaving the neck freely mobile in all directions.

The advantages of this pillow are:

(*a*) The patient's weight provides the counter-traction.

(*b*) The angle of pull is a "natural" one, thus avoiding strain on the back of the operator.

(*c*) The build of the patient governs the amount of traction applicable, relating it to the conformation of the neck.

(*d*) It is inexpensive.

Hillcrest, Natal. PHILIP H. DALGLEISH.

ERYTHROCYTE ENZYME DEFICIENCY IN UNEXPLAINED KERNICTERUS

SIR,—Kernicterus in full-term infants in Singapore is not uncommon. The pædiatric unit of the General Hospital admits approximately 40 infants per annum in whom the central-nervous-system damage is already present, and some other cases with a high serum-bilirubin requiring exchange transfusion. The majority of these cases are not due to blood-group incompatibility.[1,2] In some cases there is a family history of severe neonatal jaundice which has been fatal or has left residual central-nervous-system damage.

The mother of such a family in which 3 infants were so affected has been investigated for a hæmolytic anæmia which was found to be associated with deficiency of glucose-6-phosphate-dehydrogenase in her erythrocytes.[3] In this lady the precipitating agent was either pyridium or sulphamethoxypyridazine, but many other substances have been reported as causing this syndrome (primaquine, sulphanilamide, acetanilide, phenylhydrazine, sulphoxone, phenacetin, acetylsulphanilamide, sulphacetamide, thiazolsulphone). The same enzyme deficiency is found in favism.[4] This family had previously been investigated by us but no enzyme studies were performed and no explanation was found for the severe jaundice in the affected infants.

The blood of full-term infants with clinical features similar to those of the affected infants in the above family have been examined for glucose-6-phosphate-dehydrogenase activity by a simple colorimetric method devised by Motulsky and Campbell (see Vella[5]). Blood-group incompatibility was excluded in all cases. All infants were seen and examined clinically during the acute episode of jaundice by one of us. The clinical diagnosis of kernicterus was confirmed by necropsy in those children who died and by neurological sequelæ in those who survived the neonatal period. The results in 14 cases show that enzyme activity was absent or deficient in 13:

Case no.	*Ethnic group*	*Sex*	*Glucose-6-phosphate-dehydrogenase*
1	Chinese	Female	Absent
2	Chinese	Female	Absent
3	Chinese	Male	Absent
4	Chinese	Male	Absent
5	Chinese	Male	Absent
6	Chinese	Male	Absent
7	Chinese	Male	Absent
8	Chinese	Male	Absent
9	Chinese	Female	Intermediate
10	Chinese	Female	Absent
11	Chinese	Female	Absent
12	Chinese	Female	Absent
13	Malay	Male	Absent
14	Chinese	Female	Present

Enzyme activity was *absent* when decolorisation did not occur, in duplicate estimations, before 100 minutes. It was *present* when decolorisation occurred between 30 and 70 minutes, and *intermediate* when decolorisation occurred repeatedly at about 100 minutes.

Case 3 was interesting because this infant was one of male twins with dissimilar blood-groups. He died 2 days after admission, aged 8 days, and the diagnosis of kernicterus was confirmed at necropsy. His brother was healthy with only slight jaundice and normal enzyme activity and has progressed normally. It is probable that this syndrome of unexplained severe neonatal jaundice causing kernicterus is in many cases the result of sudden hæmolysis in infants whose erythrocytes have this inherited abnormality. The factor (or factors) precipitating hæmolysis is at present unknown. Hæmatological observations and results of an investigation to determine the responsible agent in these infants will be published later.

The kernicterus syndrome in Singapore occurs predominantly amongst Chinese infants. One of us has examined cord-blood samples from infants born in Singapore and found an incidence of glucose-6-phosphate-dehydrogenase deficiency in 2 (2·6%) out of 76 specimens from Chinese males. A

1. Maycock, H. G. T., Gibson-Hill, M. M. H. *Med. J. Malaya*, 1954, **8**, 343.
2. Wong, H. B. *Arch. Dis. Childh.* 1957, **32**, 85.
3. Vella, F., Phoon, W. O. *Med. J. Malaya*, 1959, **13**, 309.
4. Beutler, E. *Blood*, 1959, **14**, 103.
5. Vella, F. *ibid*, p. 298.

deficiency was also found in 3 (4·7%) out of 63 male adult Indians. It is therefore probable that the factor precipitating hæmolysis is related to traditional Chinese methods of caring for the mother and baby during the puerperium.

This syndrome undoubtedly belongs to the group of enzyme-deficiency hæmolytic anæmias discussed by Larizza et al. (March 12). In our infants the presenting symptom is severe jaundice which often kills before the hæmoglobin falls very low. This is presumably due to the immature liver function during the first week of life.

We are grateful to the Director of Medical Services in Singapore for permission to publish this report.

Pædiatric Unit,
General Hospital, Singapore. GWEN D. SMITH.

Department of Biochemistry,
Faculty of Medicine,
University of Malaya in Singapore,
Singapore. F. VELLA.

SERUM THROMBOCYTOPOIETIC ACTIVITY IN IDIOPATHIC THROMBOCYTOPENIC PURPURA

SIR,—We reported earlier that the serum of thrombocythæmic [1] and some thrombocytopenic [2] patients contained a factor, called thrombopoietin, capable of inducing a significant thrombocytosis of several days' duration in mice.

This factor is retained by a dialysing membrane, is destroyed by trypsin, runs with the β-globulins in electrophoresis, and is counteracted by normal human serum in the mouse.[1 2] We concluded that the biological assay used in our experiments indicated the equilibrium between the thrombopoietic factor and its biological inhibitor(s), and that this equilibrium was much disturbed in some pathological conditions.

After these observations, sera from 20 thrombocytopenic patients were tested, each on two occasions, except in a patient with hæmoblastosis and another with symptoms of hypersplenism.

0·2 ml. of fresh serum was given intravenously to 4–6 mice. Direct platelet-counts were made by phase-contrast microscopy before and 48 hours after the injection. When the platelet-count increased by more than an average of 30% the result was denoted as positive, and changes of less than 30% were negative.

Results are as follows:

	Positive	*Negative*
Cases with hypoplastic or aplastic megakaryocytopoiesis		
Hæmoblastosis	2	3
Carcinomatosis	1	..
Idiopathic panmyelopathy	1	2
Cases with hyperplastic megakaryocytopoiesis		
Acute idiopathic thrombocytopenic purpura	3	..
Chronic idiopathic thrombocytopenic purpura	1	4
Cirrhosis of the liver with hypersplenism	3	..

The serum of subjects with physiological thrombocytopoiesis is "negative".

Although the results of individual cases were reproducible, it seems that the thrombocytopoietic activity was variable even under seemingly similar conditions. However, serum samples from patients with *untreated acute* idiopathic thrombocytopenic purpura (I.T.P.) showed *enhanced* activity. The defect in acute I.T.P. is, therefore, something other than thrombopoietin deficiency. This enhanced activity was, however, no longer demonstrable in our 2 cases in which thrombopoietic activity was determined 36–48 hours after starting prednisone therapy (75–100 mg. per day).

Briggs and Verstraete [3] lately tabulated some differences between acute and chronic I.T.P. Unlike sera in acute I.T.P., sera from chronic I.T.P. cases, with 1 exception, did not show demonstrable thrombocytopoietic activity.

In agreement with these results, Schulman et al.[4] have recently noted that in a case of plasma-factor dependent chronic I.T.P. the plasma of an acute I.T.P. patient was able to elicit thrombocytosis. On the other hand, even repeated infusions of plasma from a patient with essential thrombocytosis failed to induce remission in a case of acute I.T.P. (Cochrane, see discussion to Schulman et al.[4]).

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First Department of Medicine,
Szeged University Medical School,
Szeged, Hungary. I. CSERHÁTI
K. RÁK.

PREDICTION OF OPERATIVE BLEEDING IN HÆMOPHILIA

SIR,—Owing to the difficulty in measuring the exact level of antihæmophilic globulin in hæmophilic blood, elective surgery in these patients is liable to be hazardous.

The simple method (which can be carried out within half an hour of obtaining a blood sample) described in the accompanying table, which gives the final balance between the

RELATION BETWEEN THE SUBSTRATE CLOTTING-TIME AND OPERATIVE BLEEDING

Patient	Operation	Substrate clotting-time*	Bleeding
A	1. Ureter transplantation	20	Controllable
	2. Ectopic bladder excision	63	Excessive
B	Tracheostomy	12	Normal
C	Cataract	11½	Normal
D	Tonsillectomy	16	Normal

* Blood sample, obtained immediately before the operation from a vein other than that used for the administration of A.H.G., was tested by a person who had no previous knowledge of the amount of A.H.G. injected. The plasma, after being tested with $Al(OH)_3$ suspension, was incubated *undiluted* with equal volumes of normal serum (1 : 10), platelet suspension, imidazole buffer pH 7·3, and 0·05 *M* $CaCl_2$. After 6 minutes, 0·1 ml. of the mixture, together with 0·1 ml. 0·025 *M* $CaCl_2$, was added to 0·1 ml. substrate (*patient's* plasma), recording the clotting-time.

activity of antihæmophilic globulin and that of Bridge anticoagulant,[6] was thought to provide a good index to changes in the pathological defect. Accordingly, it was used on five occasions in order to test its suitability in indicating the safety of operative procedure after antihæmophilic-globulin therapy. The substrate clotting-times obtained and the amounts of bleeding recorded are shown in the table.

From these results, it is now reasonable to recommend that this simple test should be utilised in controlling and timing surgery; if the clotting-time of a preoperative blood specimen is found to be less than 20 seconds, surgery can be proceeded with, but if the time exceeds 20 seconds further antihæmophilic globulin must be resorted to before doing so.

Blood Transfusion Centre,
Brentwood, Essex. F. NOUR-ELDIN.

"PSYCHOLOGICAL OVERLAY"

SIR,—May I be allowed to make a plea—not on behalf of my fellow nurses, but for our patients?

It is becoming increasingly common these days to state on a patient's notes—usually after many months of treatment—that there is a "large psychological overlay". Perhaps the doctors are sometimes right—and I have particularly in mind the prevalent "slipped disc"—but if you were strictly honest you should more often admit that either your diagnosis was wrong or your treatment was a failure.

A "psychological overlay" is a very convenient umbrella under which to shelter, but from the patient's angle it is a complete write-off. From now on he is a neurotic; the trouble is with himself. The pain exists not in his back but in his mind, and he is a waster of precious time, for until he decides for himself that he is going to get better there is nothing else to be done.

1. Kelemen, E., Cserháti, I., Tanos, B. *Acta hæmatol., Basel*, 1958, **20**, 350.
2. Rák, K., Cserháti, I., Kelemen, E. *Med. Exp., Basel*, 1959, **1**, 125.
3. Briggs, D. K., Verstraete, M. International Textbook of Allergy; p. 544 Oxford, 1959.
4. Schulman, I., Pierce, M., Lukens, A., Currimbhoy, Z., Fort, E. *Amer. J. Dis. Child.* 1959, **98**, 633.
5. Nour-Eldin, F. 7th European Congress of Hæmatology, London, September, 1959.
6. Nour-Eldin, F., Wilkinson, J. F. *Brit. J. Hæmatol.* 1958, **4**, 38, 292.

If after all the doctor's skill and care the patient is nothing bettered but rather made worse, could doctors not be more honest about it? Would they care to be known as "psychologically overlaid"? I know I wouldn't.

Slough. MARY KAY.

BLOOD-GROUPS AND DISEASE

SIR,—I should like to draw attention to certain points which may be of importance in evaluating the results of studies on the distribution of blood-groups in different diseases.

(1) *Absence of a basic idea.*—Investigations on the distribution of the blood-groups are generally performed without a working hypothesis. The frequencies obtained are then compared with those of a control material or an entire population. The significance of the differences, moreover, is calculated by various statistical methods.

"Statistically significant" differences in these circumstances are affected by the number of factors considered in the investigation. In blood-group studies the material is divided into at least four (often eight or more) parts, depending on the number of blood-group factors observed. The material can be divided still further by the patients' age, year of birth, sex, or any other easily recognisable attribute. The number of the combinations can rise to the hundreds, but generally only a part of them are reported.

It is only to be expected, then, that "statistically significant" differences will be established in nearly every material. It is naturally impossible to predict the combinations in which the differences will occur, nor can these differences usually be established in other authors' materials.

This has happened, for example, in the investigation by Yates and Pearce [1] in which it was found that the blood-group distribution of astrocytomas changed after 1945. At first the authors failed to find any major differences from the control material. Small manipulation, however, brought out a significant difference in the O group when the material was divided (obviously independently of the patient's age) by the year of examination.

This is the procedure often applied in clinical-statistical studies. Provided there are sufficient factors to be examined, the result is that differences and coincidences are almost always encountered. Clinical experience and common-sense, however, usually reveal the real reason for these differences and obviate the need for mathematical study. There is no sentiment involved in the study of blood-groups, and little experience to draw on. It is hardly surprising, then, that common sense is often forgotten in analysing the results.

An unexpected distribution of blood-groups is in fact comparable with the way the cards fall when dealt. For a player to get a hand of 13 spades is rare but not impossible. The dealer cannot be blamed (though he might be suspected); but the result, statistically confirmed, is not published in a bridge magazine.

(2) *Selective factors.*—One selective factor was discussed above: the material is divided up in order to make the differences emerge. Mention is omitted of previous unsuccessful attempts in dividing up the material.

It must also be regarded as probable that the authors have at their disposal several sets of material and concentrate on those which show up the differences most distinctly.

Finally, it is certain that the materials in which differences are shown tend to appear in print more readily than those in which no differences are found. This may lead to a flow of reports resulting finally in the conclusion that the differences observed are correct. Indeed, the publication of another study indicating differences in agreement with the study published is more likely than a new report finding no differences. Courtesy alone may prevent the publication of the latter. When somebody ultimately collects all the materials reported in the world literature, the point is established, Q.E.D.

In general, scientific research without a working hypothesis and basic idea will hardly ever produce results, whatever it may appear to do at first glance. This is likely to be true also of blood-group research.

Finnish Red Cross Blood Transfusion Service, Helsinki. H. R. NEVANLLINA.

1. *Lancet*, 1960, i, 194.

Parliament

QUESTION TIME

Children and the Courts

IN answer to a question Mr. DENNIS VOSPER, an undersecretary of State to the Home Office, said that between Jan. 1, 1950, and Dec. 31, 1959, 32,550 children were brought before juvenile courts in England and Wales as being in need of care or protection and were dealt with in the following ways:

Ordered to be sent to an approved school ..	2385
Committed to the care of a fit person	13,577
Parent ordered to enter into a recognisance to exercise proper care and guardianship ..	683
Supervision order alone	11,542
No order made	4363

Mr. ALAN BROWN: Is the Minister aware that Britain is now among the minority of countries in which child victims of lack of protection or of cruelty or neglect can still be brought before courts of summary criminal jurisdiction? Would he consider setting up courts of guardianship before which this class of children could be brought? Mr. VOSPER: The Ingleby Committee is shortly to report. It is considering the whole question and I would rather not make a further comment at this stage.

Miss ALICE BACON: Is the Minister aware that magistrates in juvenile courts find themselves in an extremely difficult position because they have nowhere to send juvenile offenders on remand? Is he aware that recently a magistrate said that he never slept at night after he had been working at the juvenile court? Does not the Minister agree that even before the Ingleby Committee reports one of the most urgent things to be considered is the provision of more remand homes?—Mr. VOSPER: A Bill is before the House dealing in detail with this subject. The Home Secretary is giving consideration to that aspect of the matter in advance of the Ingleby Committee recommendations.

Mr. SYDNEY SILVERMAN: Should not the right hon. Gentleman also be asked to consider whether the juvenile courts are in any difficulty at all? In the case of very young people, juvenile persons who are not yet convicted and are on remand, if there is any real difficulty in finding a suitable place for them to go, is it not infinitely better to send them home than to send them to jail?—Mr. VOSPER: In general there is no difficulty in finding a place in a remand home. The difficulty arises with those people who are so unruly that the remand home itself is not suitable.

Consultants' Letters

Mr. W. GRIFFITHS asked the Minister of Health whether he was aware that the National Health Service patients of some general medical practitioners in Manchester, having been referred to certain consultants, were not seen by these consultants but by a registrar; and what steps were taken to ensure that all consultants attended regularly and promptly the sessions at the hospital in accordance with their contracts.—Miss PITT replied: If the hon. Member will give me details of what he has in mind, I will have inquiries made. Mr. GRIFFITHS: Is the hon. Lady aware that these complaints originate not from me but from members of the medical profession in Manchester, and from patients? Is she further

aware that I sent her department copies of specific allegations made by a general practitioner—a family doctor—who said:

"I am sick and tired of getting hospital reports back signed by the hospital registrar *p.p.* the consultant. It is not the registrar's opinion I want, it is the consultant's."

These are the sort of complaints we are getting, reinforced by many letters from patients who, after attending a number of times at the outpatients' department, suddenly discover, sometimes by accident, that they are being seen not by the consultant they imagined they were seeing but by the registrar—and sometimes even by a house-man.—Miss PITT: I have seen a newspaper cutting which contains that statement, but I do not think I have seen any official letter from the hon. Member with details amplifying such a statement. If he has such details, I shall be glad to look into them. In any case, it is for the consultant to arrange how his own clinic should be held.

Dr. EDITH SUMMERSKILL: In the event of a consultant not attending a clinic, is a deduction made in his remuneration?—Miss PITT: Not to my knowledge, but I should like notice of that question.

Pay of Midwives

Dr. SUMMERSKILL asked the Minister whether he was aware that domiciliary midwives were on call 123 hours a week for a weekly salary of £12; and whether he would take immediate action to improve these conditions.—Mr. WALKER-SMITH replied: Pay and conditions of service of midwives are matters in the first instance for the Nurses and Midwives Whitley Council.

Poliomyelitis in the Vaccinated

In answer to a question, Mr. DEREK WALKER-SMITH, the Minister of Health, gave the following figures for cases of poliomyelitis in 1958 and 1959:

Year	Group	Paralytic		Non-paralytic		Totals
		<15 yr.	15 yr. and over	<15 yr.	15 yr. and over	
1958	All cases	959	458	428	147	1992
	No. among vaccinated†	88	4	83	3	178
1959*	All cases	512	220	215	74	1021
	No. among vaccinated†	76	10	56	14	156

* Provisional figures.
† Two or more injections of poliomyelitis vaccine.

Expenditure on Social Services

The total current and capital expenditure on social services in the United Kingdom in 1959–60 was £3720·6 million (£1455·1 million from the Central Government, £1029·6 million from National Insurance Funds, and £1420·7 million from local authorities). Current and capital expenditure by all public authorities on the social services expressed as a percentage of the national income was 17·75% in 1951 and 19·5% in 1959.

N.H.S. Prescriptions

The average cost of prescriptions provided under the National Health Service in February, 1960, was approximately 6*s.* 11*d.*

Local Authorities' Mental Health Services

Of 146 authorities 120 have submitted to the Minister of Health their formal proposals for the development of community mental health services, and 14 have done so informally.

Senior Registrars

On July 1, 1959, there were 120 registrars who had completed their training, of whom 78 were in their sixth or later year.

Shortage of Dietitians

On Aug. 1, 1959, 110 posts for therapeutic dietitians in the National Health Service were unfilled.

Obituary

CONRAD MEREDYTH HINDS HOWELL

M.A., D.M. Oxon., F.R.C.P.

Dr. C. M. Hinds Howell, consulting physician St. Bartholomew's Hospital and to The National Hospital, Queen Square, died on May 9, at the age of 83.

The son of Conrad Goodriche Howell, a barrister-at-law and an official of the Ecclesiastical Commission, he was educated at Marlborough, Trinity College, Oxford, and St. Bartholomew's Hospital. At Oxford he received a first-class in the honour school of natural science (physiology), and he entered Barts as a senior entrance scholar. There he won the Kirkes scholarship and gold medal and the Brackenbury and Lawrence scholarships before qualifying in 1902. After holding junior appointments at Barts and at Queen Square, he was appointed to the staff of the Great Northern (later Royal Northern) Hospital in 1908 and The National Hospital in 1912. He was elected F.R.C.P. in 1912. In 1920 he became assistant physician at Barts and soon afterwards he resigned his appointment at the Royal Northern. He was promoted physician to Barts, and retired from the active staff in 1937 at the retiring age of 60 which was in force at that time. During the war he returned to work in the Barts E.M.S. section hospital at St. Albans. He remained on the active staff at The National Hospital until 1942 and for some years he was dean of its postgraduate school.

Dr. Hinds Howell gave much to the Royal College of Physicians of London, where he held the offices of counsellor, censor, senior censor, and treasurer. He was the college representative on the committee of management of the Conjoint Board for twelve years, and was chairman for four years. He was an examiner for the universities of Oxford and London and for the Conjoint Board. As president of the section of neurology of the Royal Society of Medicine in 1935 he gave an address on arachnoiditis. He was a founder member of the Association of British Neurologists and in 1946 was president of the British branch of the International League against Epilepsy.

J. A. T. writes:

"Dr. Hinds Howell was primarily a neurologist but he was also a general physician of wide knowledge and experience, and he was a stimulating teacher with a pleasing wit. He developed a remarkable facility for injecting the gasserian ganglion under general anæsthesia, a difficult procedure but one in which he rarely failed. His kindness and sympathy to patients was an inspiration to a succession of his house-physicians. During his late fifties and early sixties he had a number of illnesses, but he made an excellent recovery and during the last twenty years of his life he was full of vigour. He was working till a week before his death.

"As a young man he was a keen cricketer and he was a member of the M.C.C. for sixty years. He had been in the Marlborough first XI and for many years captained 'the Past' in the annual Barts Past *v.* Present cricket match. Later on he became a keen fisherman and a good shot. He was also interested in painting and philately."

A further tribute comes from G. G.:

"Hinds Howell (Con to his friends) was an excellent teacher not only in neurology but also in medicine, as he taught the

general principles in a way which made the students remember them and better able to appreciate details taught by the other physicians. As neurology became more and more specialised he was persuaded to start a neurological consultative clinic at which he saw patients referred to him by his colleagues. This experience convinced him of the desirability of having a neurologist on the staff when he retired, and he welcomed the appointment of Dr. Denny-Brown.

"He was good at all games and played golf in the annual staff *v.* Students match until the outbreak of the war."

Dr. Hinds Howell married Mabel Gulland, an Edinburgh medical graduate, in 1905. She died in 1958, and he is survived by three sons, one of whom is Dr. C. A. Hinds Howell.

PHILIP ELLMAN

F.R.C.P.

Dr. Ellman, who died on May 10, was consulting physician to the rheumatism unit of St. Stephen's Hospital, Fulham, and consulting physician for diseases of the chest to the North-East Metropolitan Regional Hospital Board. As his appointments show, he had two specialties, and he made substantial contributions to each.

After qualifying from the Manchester medical school in 1923, he continued his studies abroad in Frankfort and in Lausanne, where he took the degree of M.D. and held a research scholarship in clinical medicine at the cantonal hospital. On his return to this country he held clinical assistantships at the Brompton Hospital, the Royal Chest Hospital, and the National Heart Hospital in London. He was also for a time assistant medical officer at Colindale Hospital and the West Middlesex Hospital and physician to the East Ham and Battersea Chest Clinic.

His work as physician to the St. John Clinic and Institute of Physical Medicine in Pimlico gave scope for his interest in the rheumatic diseases. With Sir Leonard Hill, who was director of research at the institute, he edited a course of lectures given by the staff which was published under the title of *The Rheumatic Diseases*. When the institute and clinic were demolished to make room for a new housing estate, he joined the rheumatic unit at St. Stephen's Hospital. F. B., who was his colleague there, writes:

"This was a special unit sponsored by Sir Frederick Menzies, then chief medical officer of the London County Council. We believed it to be a pioneer scheme in which a special unit was built up in a general hospital, and in which, for the first time, medical specialists, medical auxiliaries, almoners, and patients worked together as a team. Ellman started annual weekend courses for general practitioners and those working for high qualifications, and he continued until a month before he died to be their stimulator and integrator. He loved his bedside teaching of the medical students who came to us from the Westminster Hospital.

"It was he who, I believe, coined the term 'rheumatoid disease'. He published papers on the 'rheumatoid lung'. He would argue heatedly if anyone doubted his evidence—as well remember from the occasion when I pointed out to a foreign visitor the interesting geographical distribution of this condition, so common on his side of the ward, so rare on mine. Many years ago he recognised the importance of psychological factors in 'fibrositis'. It might be said that he was more interested in nomenclature than in management; but he was a good physician, and his papers on Morquio-Brailsford's disease, arthromyodysplasia congenita, acromegaly, and Felty's syndrome have found a place in the reference libraries of the world.

"At St. Stephen's we will miss this lovable man—his zeal, his enthusiasm, his interest in teaching, and his capacity for filling his day so full that he really made us feel that he was justified in continually putting off until the morrow matters that we wanted to settle on the day."

In his other specialty he also won the respect and affection of his colleagues. One of them, J. R. B., writes:

"Not only did Ellman stimulate his associates to do original work, but also he wrote extensively himself. He made notable contributions particularly where rheumatology and diseases of the chest meet. His description of the pulmonary manifestations of the diffuse collagen diseases added an important link in the chain of knowledge of pulmonary infiltrations. His chest unit at Plaistow was a model of its type, and the remarkable variety of excellent clinical material there was evidence of the breadth of his interests, and of his enthusiasm for accurate and complete diagnosis."

Outside this country he was known to many as editor of the *British Journal of Diseases of the Chest*. T. H. S. writes:

"This was a project to which he gave his whole-hearted attention, and the way in which he chose and selected his contributors was a testimony to his knowledge in this branch. He will best be remembered by his energy and enthusiasm, which were so often a stimulus to others and gave a delightful turn to his character. In his professional life I suppose the one thing he would have been proudest to be called is a good doctor, and this he certainly was."

Dr. Ellman leaves a widow, a son, and a daughter.

Appointments

BRIERLEY, J. S. W., M.B. Leeds: assistant M.O.H. and assistant school M.O., Rotherham.
LINGWOOD, MURIEL M., M.B. Durh., D.C.H.: assistant M.O., Kingston upon Thames and Wimbledon areas, Surrey.
MCLEAY, CHRISTINA J., M.B. Edin.: assistant M.O.H. and school M.O., Smethwick.
MATHESON, K. W., M.B., B.SC. Edin., D.C.H., D.P.H.: deputy M.O.H., Nottingham.
PIPER, G. W., M.B. Lond., D.P.H.: M.O.H., Holborn, London.
SCOTT, O. L. S., M.B. Cantab., M.R.C.P.: honorary dermatologist, French Hospital and Dispensary, London.
SHARP, MARY K., M.R.C.S.: assistant M.O. and school M.O., Morley division, Yorkshire.
SNAITH, A. H., M.B. Durh.: assistant M.O., Kingston upon Thames and Wimbledon areas, Surrey.
SPEIRS, N. T., M.B., B.SC. Edin., D.M.R.D.: consultant radiologist, East Lothian group of hospitals.
*TOWNSEND, MARY, M.B. Lond., M.R.C.P., D.C.H.: senior M.O. in charge of maternity and child welfare and school M.O., Dorset.
WATSON, J. A. G., M.B. Lond., D.P.H.: deputy M.O.H. and deputy principal school M.O., Oxfordshire.

Sheffield Regional Hospital Board:

ESPIR, M. L. E., M.B. Cantab., M.R.C.P.: part-time consultant neurologist, Leicester group of hospitals.
HUGHES, HUGH, M.B. Birm.: senior casualty officer, Scunthorpe and District War Memorial Hospital.
WARDLE, C. J., M.B. Lond., D.P.M.: consultant in children's psychiatry, North Lincolnshire.

Western Regional Hospital Board, Scotland:

COYLE, T. C., M.B. Glasg.: assistant in laboratory medicine, area laboratory, Dumfries and Galloway Royal Infirmary.
HAMILTON, CHRISTINA M., M.B. Glasg., D.P.M.: assistant psychiatrist, Eastern District Hospital, Glasgow.
MILLER, J. H., M.B. Glasg., F.R.C.S.E.: consultant surgeon, Glasgow Royal Infirmary.
STIRLING, G. S., M.B. Aberd., D.P.M.: consultant psychiatrist, Crichton Royal Mental Hospital, Dumfries.

Colonial Appointments:

ACANNE, JEAN, M.B. N.U.I.: house-officer, Trinidad.
BRINKERT, H. C., M.D. Amsterdam: M.O., Nigeria Northern Region.
CHIPPENDALE, IAN, M.B. Cantab.: M.O., Hong Kong.
CORDICE, G. J., M.B. Aberd.: M.O.H., St. Vincent, Windward Islands.
DALTON, N. T., M.B.: M.O., Nigeria Northern Region.
FORBES, G. I., L.R.C.P.E., D.T.M. & H., D.P.H.: M.O., Hong Kong.
HAMILTON, D. M., B.M. Oxon, F.R.C.S.: surgeon, medical department, Aden.
HARTHOORN, HELENA J., M.B. Lond., D.OBST.: M.O., Uganda.
HOLMES, R. G., M.B. Lond.: M.O., Uganda.
JOHNSTONE, GEORGE, F.R.F.P.S.: surgical specialist, Tanganyika.
MCCLEERY, C. H., M.B. Lond.: M.O., Tanganyika.
MATHEWS, T. C. H., M.R.C.S., D.T.M. & H., D.P.H.: senior M.O., Kenya.
RENTON, R. L., M.B. Aberd.: M.O., Nigeria Northern Region.
WEBB, R. A. J., M.B. Lond.: M.O.H., Barbados.

* Amended notice.

Notes and News

PHARMACEUTICAL INQUIRY

THE Minister of Health has announced that the Central Health Services Council has, at his suggestion, appointed a standing committee, under the chairmanship of Lord Cohen of Birkenhead, to advise on operational research in the pharmaceutical services. Its terms of reference are:

"Having regard to the need to avoid unnecessary expenditure in the pharmaceutical services provided under Part IV of the National Health Service Act, 1946, to advise the Minister on (1) the operational research which should be undertaken in relation to those services, involving the collection of statistical, economic and socio-medical data, and on (2) the interpretation of such data."

The other members of the committee are:

Mr. E. F. Collingwood, chairman, Newcastle Regional Hospital Board; Sir Hugh Linstead, M.P., secretary, Pharmaceutical Society of Great Britain; Dr. A. Talbot Rogers, member, General Medical Services Committee; Mr. J. C. Hanbury, chairman, Allen & Hanburys, Ltd.; Mr. H. Noble, secretary, National Pharmaceutical Union; Dr. H. C. Faulkner, general practitioner, London; Dr. J. C. H. Bird, general practitioner, Usk; Dr. B. Abel-Smith, lecturer in social science, London School of Economics; Mr. L. C. H. Tippett, principal statistician, British Cotton Industry Research Association; Mr. R. Falk, managing director, Marketing Development Company; Mr. M. Perrin, member, Advisory Council on Management Efficiency, and Wellcome Foundation; Mr. G. McLachlan, secretary, Nuffield Provincial Hospitals Trust.

WORLD HEALTH ASSEMBLY

Prof. V. M. Zhdanov (U.S.S.R.), the chairman, opening the technical discussions of the thirteenth World Health Assembly, now being held in Geneva, suggested that eradication of poliomyelitis was a practical possibility. In Russia, he said "We therefore await with impatience the results of the immense programme of immunisation against poliomyelitis in the course of which it is intended in six months or a year to administer the [live virus] vaccine to not less than 80 million persons. If this experiment proves truly satisfactory, it will answer the question of whether it is possible to eradicate poliomyelitis, at any rate for practical purposes, by means of mass immunisation of the population".

At a plenary session the following six member States were elected to designate a person to serve on the Executive Board of W.H.O.: Ghana, Thailand, Jordan, Korea, United Kingdom, and Argentina. The Assembly expressed its appreciation of the invitation extended by the Government of India to hold the fourteenth World Health Assembly in India in February, 1961. The Assembly decided to extend the use of the Russian language in some W.H.O. publications.

The Committee on Programme and Budget recommended the Assembly to adopt a working budget for 1961 of $18,975,354—some 12% more than the effective working budget for 1960. Introducing the budget, Dr. M. G. Candau, director-general of W.H.O., said that eradication of communicable disease still represented the largest single item (31%) in the Organisation's regular budget; but in the long run the Organisation's most important work was still education and training.

HOSPITAL INPATIENT INQUIRY

THE first part of a new report on the Hospital Inpatient Inquiry has appeared.[1] This series, designed to provide supplementary information on the types of patient and disease treated, is published jointly by the Ministry of Health and the General Register Office.

Part I gives summaries for selected conditions for 1958 and certain figures for 1955-57, which will be amplified in part II. The survey is based on a 10% sample of discharges (including deaths) from National Health Service hospitals. In England and Wales in 1958 the total discharges amounted to $3^1/_2$ million. Although for many conditions the number of discharges has increased since 1955, this may be due not to increasing prevalence, but to other factors such as more widespread admission to hospital. A table shows the perio patients have to wait for admission to hospital for different condition For neoplasms of the lung in males, for example, 52% of patien are admitted immediately and 91% within a month. For tonsi and adenoids, however, only 3·2% are admitted immediately an 23% within a month; 21% have to wait over six months for admis sion. There were 75·9 admissions for maternity care per 100 birth The hospital-delivery-rate averaged 57·5% in England and Wales i 1958, the highest rate being recorded in Greater London (69·1%

1. Ministry of Health and General Register Office. Report on Hospital Inpatient Enquiry: Part 1. H.M. Stationery Office. 1960. p. 14. 1s. 6d.

CERTIFICATION

THE report of the National Insurance Advisory Committee reaffirms the principles of certification for sickness or confine ment benefit with which practitioners are familiar, though i notes in passing that some doctors might, to their own benefit acquaint themselves closely with the regulations. The committe rejected a proposal that there should be a list of specifie conditions for which the doctors might issue certificates o more than one week's duration from the beginning. Becaus under its terms of reference its deliberations were restricted t certification for National Insurance purposes, the committe expressed no opinion on suggestions that modifications of th National Insurance certificates might simplify their use fo other purposes. This is a pity, for the demand for extr certificates wastes time in practice. The Ministry might b invited to think again on this point, giving its committee wider brief.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued th following new supplementary list of approved names:

Approved name	*Other names*
Amphotericin	Polyene antibiotics isolated from a strain of *Streptomyces* species, referred to as *Streptomyc nodosus* (specific substances are designated by terminal letter; thus, Amphotericin B) Fungizone is Amphotericin B
Benzonatate	2-(ω-Methoxypolyethyleneoxy)ethyl *p*-butylamin benzoate Tessalon
Benzthiazide	3-Benzylthiomethyl-6-chloro-7-sulphamoylbenzo-1:2:4-thiadiazine 1:1-dioxide Fovane
Chlormidazole	1-*p*-Chlorobenzyl-2-methylbenzimidazole
Chlorzoxazone	5-Chlorobenzoxazolin-2-one
Cinnarizine	1-*trans*-Cinnamyl-4-diphenylmethylpiperazine
Diethylpropion	α-Diethylaminopropiophenone Tenuate is the hydrochloride
Guanethidine	1-(2-Guanidinoethyl)azacyclooctane Ismelin is the sulphate
Itramin tosylate	2-Nitratoethylamine toluene-*p*-sulphonate Nilatil
Methandienone	17β-Hydroxy-17α-methylandrosta-1:4-dien-3-one Dianabol
Methdilazine	10-(1-Methyl-3-pyrrolidinylmethyl)phenothiazine
Metronidazole	1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole Flagyl
Nealbarbitone	5-Allyl-5-neopentylbarbituric acid Censedal; Nevental
Paromomycin	An antibiotic produced by *Streptomyces rimos forma paromomycinus* D-Glucosaminedeoxystreptamine D-ribosediamin hexose Humatin is the sulphate
Phenethicillin	6-(α-Phenoxyproprionamido)penicillanic acid (1-Phenoxyethyl)penicillin Broxil is the potassium salt
Pralidoxime iodide	Picolinaldoxime methiodide Protopam
Sodium ipodate	Sodium β-(3-dimethylaminomethylenamino-2:4: triiodophenyl)propionate Biloptin
Spironolactone	β-(7α-Acetylthio-17β-hydroxy-3-oxoandrost-4-en-17α-yl)propionic acid lactone Aldactone
Sulphinpyrazone	1:2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3:5-dione Anturan
Thioproperazine	2-Dimethylsulphamoyl-10-[3-(4-methylpiperazin-1-yl)-propyl]phenothiazine Majeptil is the methanesulphonate

Proprietary name	*Approved name reference*	*Proprietary name*	*Approved name reference*
Aldactone	Spironolactone	Anturan	Sulphinpyrazo
Biloptin	Sodium ipodate	Broxil	Phenethicillin
Censedal	Nealbarbitone	Dianabol	Methandienon
Flagyl	Metronidazole	Fovane	Benzthiazide
Fungizone	Amphotericin	Humatin	Paromomycin
Ismelin	Guanethidine	Majeptil	Thioproperazi
Nevental	Nealbarbitone	Nilatil	Itramin tosyla
Protopam	Pralidoxime	Tenuate	Diethylpropio
Tessalon	Benzonatate		

1. Doctors' and Midwives' Certificates for National Insurance Purpose report of the National Insurance Advisory Committee. H.M Stationery Office. 1960. Pp. 12. 1s.

A YOUNGHUSBAND TYPE?

IN 1956 the Manchester Regional Hospital Board, with the helpful connivance of such interested parties as the University of Manchester, the Ministry of Health, and the Institute of Almoners, started an experimental training scheme for "hospital welfare workers". Almoners were scarce in the region, and it was hoped that by this means people with suitable personality and experience who did not necessarily have academic qualifications could be trained to deal independently with the straightforward needs of patients. The almoners, as qualified case workers, could reserve their time and energy for patients with complex personal problems. Since then the Younghusband Committee have included in their proposed revision of the structure of the social services a "general purpose social worker" who might well have a good deal in common with Manchester's hospital welfare worker, though his, or her, activities would of course not be limited to the hospital. Manchester's experimental training course may thus prove to have been an involuntary modest pilot scheme, and the report of its first three years by Mrs. Gray, the tutor for the scheme, will find attentive readers outside the Manchester region.[1]

The course was open to men and women between twenty-one and forty-five though older people were considered. There was room for only 8–10 students; but despite many inquiries (968 in 1958), the selection committee found no great untapped reserve of potentially good workers and could not have filled more places had they been available. The course lasted twelve months and included practical work in almoners' departments as well as theoretical studies. The trainees were paid a salary of £300 p.a. Of the 12 who successfully completed the course in the first two years 10 are now working—5 with almoners and 5 on their own. Even with this small number there seem to have been difficulties in arranging for practical work. At the end of their course workers were allocated to hospitals within the region by a subcommittee of the board on the recommendation of the tutor. This system has defects as well as merits, and though perhaps appropriate at this experimental stage, it would presumably be discarded in any permanent scheme.

POISONS LIST

THE following substances (and their salts or esters) have been added to part I of the Poisons List [2]:

Acetylcarbromal.
Androgenic and oestrogenic substances.
Benzoestrol.
Derivatives of stilbene, dibenzyl or naphthalene with oestrogenic activity.
Steroid compounds with androgenic or oestrogenic activity.
Azacyclonol.
Benactyzine.
Benzethidine.
3-Benzylhydrazinocarbonyl-5 methylisooxazole.
Bromvaletone.
Captodiame.
Carbromal.
2-*p*-Chlorophenyl-3-methylbutane-2:3-diol.
Chlorpropamide.
Cyclophosphamide.
Dimenoxadole.
Furethidine.
4-Hydroxymethyl-2:2-di*iso*propyl-1:3-dioxolan.
Hydroxyzine.
Imipramine.
Mannomustine.
Mephenesin.
Meprodamate.
Metformin.
Methocarbamol.
α-Methyl-phenethylhydrazine.
Methyl phenidate.
Norcodeine.
Normorphine.
Phenazocine.
Phenelzine.
Phenformin.
Phenmetrazine.
Pipradrol.
Thalidomide.
Zoxazolamine.
Alkaloids:
Rauwolfia, alkaloids of.
Anti-histamines:
Buclizine.
(*p*-Chlorophenylpyrid-2-yl-methyl) 2-dimethylaminoethyl ether.
1-(4-*p*-Chlorophenyl-3-phenyl-but-2-enyl)-pyrrolidine.
Chlorpheniramine.
Clemizole.
Cyclizine.
1-Dimethylamino-3-phenyl-3-(2-pyridyl)-propane.
Diphenylpyraline.
Doxylamine.
Isothipendyl.
Mebhydrolin.
Meclozine.
Thenalidine.
Triprolidine.

For the item "3-(10-Phenothiazinyl)propane substituted in the 1-position; its salts; derivatives of 3-(10-Phenothiazinyl)propane substituted in the 1-position; their salts" there shall be substituted the item "Phenothiazine, derivatives of; their salts; except promethazine, its salts and its molecular compounds".

The Poisons Rules [3] have been consolidated and amended.

1. Gray, Rosemary. Training Scheme for Hospital Welfare Workers. 1960. Pp. 45. 2*s*. (From Manchester R.H.B., Cheetwood Road, Manchester, 11.)
2. The Poisons List Order, 1960. S.I. 1960, no. 698. H.M. Stationery Office. Pp. 10. 6*d*.
3. The Poisons Rules, 1960. S.I. 1960 no. 699. H.M. Stationery Office. Pp. 44. 1*s*. 9*d*.

University of Birmingham

The following titles have been conferred:

Dr. C. R. Lowe, reader in social medicine; Dr. J. M. French, honorary reader in medicine; Dr. J. P. Bull, honorary lecturer in the department of experimental medicine.

Mr. R. J. Mills has been appointed William E. Dunn research associate in the department of medicine and Mr. B. Atkins research associate in the department of pædiatrics and child health.

University of Glasgow

Dr. C. M. Fleming has been appointed to the recently established chair of administrative medicine.

Dr. Fleming, who is 56 years of age, was educated at Hillhead High School and the University of Glasgow where he graduated M.A. in 1924, M.B. in 1929, and M.D. in 1933. He became a member of the Royal College of Physicians of Edinburgh in 1945 and a fellow in 1952; he was elected a fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1959. Dr. Fleming, who has been dean of the faculty of medicine in the university since he became reader in administrative medicine early last year, joined the Department of Health for Scotland as a regional medical officer in 1937, and became a principal medical officer in 1946.

Dr. A. C. Forrester has been appointed reader in anæsthetics and Dr. E. Hutchinson reader in hæmatology.

Royal College of Surgeons of England

At a meeting of the council on May 12, with Sir James Paterson Ross, the president, in the chair, Dr. Frankis Evans, Surgeon Captain J. L. S. Coulter, Dr. E. F. Scowen, and Prof. E. C. Amoroso were admitted to the fellowship after election.

The Jacksonian prize was presented to Mr. Geoffrey Slaney and the Lady Cade medal was awarded to Group-Captain Ralph Coburn Jackson.

Postgraduate diplomas and diplomas of membership were conferred on the candidates named in the report of the comitia of the Royal College of Physicians (*Lancet*, May 7, 1960, p. 1033).

British Pædiatric Association

The following officers have been appointed:

President, Prof. A. V. Neale; president elect, Prof. A. A. Moncrieff; treasurer, Prof. A. G. Watkins; secretary, Dr. E. W. Hart.

Society of Apothecaries of London

Faculty of the History of Medicine and Pharmacy.—Dr. K. D. Keele will give the first annual students' lecture on Thursday, June 2, at 5.30 P.M. at Apothecaries' Hall, Black Friars Lane, E.C.4. His subject will be William Harvey—Pioneer of Medical Science. Admission is by ticket, obtainable from the deans of the medical schools.

Oliver Bird Lecture

Dr. J. Parizek, from the Laboratory of Physiology and Pathophysiology of Metabolism, Prague, will give this lecture on Thursday, May 26, at 5 P.M. at Guy's Hospital Medical School, London, S.E.1. He will speak on sterilisation of the male by cadmium salts.

Patrick Buxton Memorial Prize

This has been endowed in memory of Prof. P. A. Buxton, a former director of the department of entomology at the London School of Hygiene and Tropical Medicine. The first award will be made in 1961 to past or present students or members of the staff of the school. Further particulars may be found in our advertisement columns.

Congress of European Organisation for Research on Fluorine and Dental Caries Prevention

This congress will be held from June 2 to 4 in Hamburg. Speakers from this country will include Mr. R. Fearnhead, Prof. A. I. Darling, Prof. A. B. Macgregor, Mr. J. H. Fremlin, and Mr. F. L. Hardwick. Particulars may be had from the secretariat of the congress, Hamburg 20, Martinstrasse 52, Universitätskrankenhaus Eppendorf, Zahn, Mund, Kieferklinik (C II), Germany.

Doctors in Malta

Doctors in the Government medical service of Malta, who have been on strike since May 2, returned to work on May 14 (*Times*, May 16) after an agreement was reached over an appointment to the post of deputy senior medical officer.

Dental Ancillaries

A training course for dental hygienists started in Manchester last autumn. Other training units are expected to be ready this year. The General Dental Council's experimental training scheme for dental auxiliaries is planned to start in the autumn.

World Congress on the Prevention of Occupational Risks

This congress, arranged by the National Safety Institute of France, will be held in Paris from May 22 to 27, 1961. Particulars may be had from the Institut National de Sécurité, Secrétariat du IIIe Congrès mondial, 9, avenue Montaigne, Paris 8e.

European Congress of Child Psychiatry

This congress wil be held at the New School of Medicine, 45, rue des Saints Pères, Paris VI°, from Sept. 16 to 20. The theme will be maturation. A symposium on child psychoanalysis will be held at the end of the congress. Further particulars may be had from the secretary-general, Dr. D. J. Duché, Pavillon Clérambault, Hôpital de la Salpétrière, 47, boulevard de l'Hôpital, Paris XIIIe.

Proposed New Hospital for North Hertfordshire

On May 4 the North West Metropolitan Regional Hospital Board met representatives of the Baldock, Hitchin, Letchworth and Stevenage councils and the Stevenage Development Corporation to outline their plans for the hospital services for the area. It was proposed to build a new hospital with about 400 beds at Corey's Mill, Stevenage, which would serve the acute hospital needs of the area. It would become a new Lister Hospital replacing the temporary wartime hospital in Hitchin. Part of the present Lister Hospital would then become the geriatric hospital for the area and the North Herts Hospital would be reserved for maternity work. The proposals would need the approval of the Ministry of Health.

The National Hospital, Queen Square

The centenary celebrations of this hospital will be opened on Monday, June 20, at 11.30 A.M., by Mr. Derek Walker-Smith, the Minister of Health. On the following day, June 21, at 10.45 A.M. the Duke of Edinburgh will visit the hospital. Demonstrations and lectures will be given at the hospital from June 20 to 24. Neurologists from abroad who are taking part will include: Dr. Pearce Bailey (Bethesda, Maryland), Prof. T. Alajouanine (Paris), Prof. H. Gastaut (Marseilles), and Dr. Chorobski (Warsaw). Dr. Macdonald Critchley will give the centennial oration, in which he will speak on Jacksonian ideas and the future with special reference to aphasia: Sir Charles Symonds the Gowers lecture (disease of mind and disorder of brain); and Prof. Norman Dott the Victor Horsley lecture (brain, movement, and time).

By arrangement between the North East Metropolitan Regional Hospital Board and the Royal Free Hospital, some consultants and senior hospital medical officers are to attend the Royal Free Hospital for short postgraduate courses. The idea behind the scheme is to promote closer cooperation between the pathology departments of teaching and non-teaching hospitals, and to give pathologists the opportunity of learning any techniques more usually found in a teaching hospital.

Mr. L. T. Morton, the librarian of the National Institute of Medical Research, Mill Hill, London, N.W.7, has received the Marcia C. Noyes award of the Medical Library Association of America.

The United Hospitals Choir with the London Choral Orchestra will give a performance of Handel's Belshazzar on Tuesday, May 31, at 7.30 P.M., in Chelsea Town Hall, London, S.W.3. Tickets (7*s*. 6*d*., 5*s*., 3*s*. 6*d*.) may be had from Miss E. Sorensen, South Western Hospital, Landor Road, S.W.9, or at the door.

The Biochemical Society will hold a joint meeting with the Société de Chimie Biologique at the Faculté de Pharmacie, Avenue de l'Observatoire, Paris 6e, on Friday and Saturday, May 27 and 28.

The Yorkshire Society of Anæsthetists will hold a meeting on Wednesday, June 8, at 8.30 P.M. at the General Infirmary at Leeds. Dr. Shila Ransom will speak on the role of the anæsthetist in the obstetric unit.

The North of England Otolaryngological Society will hold a meeting with the Scottish Otolaryngological Society in Carlisle on Saturday, June 11, at 2 P.M.

Diary of the Week

MAY 22 TO 28

Monday, 23rd

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, W.2
5 P.M. Dr. P. L. Mollison: The Role of Complement in Blood Group Reactions. (Almroth Wright lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Prof. E. P. Sharpey-Schafer: Syncope.

MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice* Dr. H. W. Ashworth: Hobson's Choice. (Presidential address.)

Tuesday, 24th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine*. Dr. A. St. J. Dixon: Hyperuricæmic Nephropathy. Dr. C. T. Dollery: Detection of Unilateral Renal Disease in Hypertension with Diodrast ^{131}I. Dr. A. M. Joekes: Indications for Renal Biopsy.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Mr. Leonard Easton: Historical Aspects and Modern Views of Management of Retained Placenta.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Prof. Gilbert Causey: Observations on the Optical and Electron Microscopical Structure of the Skin.

Wednesday, 25th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. A. F. B. Standfast: Infection of Mice with *Bordetella* (*Hæmophilus*) *pertussis*.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Sir Russell Brock: Aortic Stenosis.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Recent Advances in the Study of Ringworm.

UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary.) Prof. Raoul Palmer: Reconstructive Surgery of Fallopian Tubes. (Litchfield lecture.)

MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology*. Prof. Jethro Gough: Recent Advances in the Pathology of Lung Diseases.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Street, Edinburgh
5 P.M. Mr. F. J. Gillingham: Stereotactic Surgery of the Brain—Therapy and Research. (Morison lecture.)

Thursday, 26th

UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Prof. P. Waser (Zürich): The Cholinergic Receptor.

UNIVERSITY COLLEGE, Gower Street, W.C.1
5 P.M. Dr. S. J. Bach: Metabolic Fate of Protein-nitrogen in the Mammal. (First of two lectures.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Prof. M. L. Rosenheim: Phæochromocytoma.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. P. D. Samman: Cutaneous Reticuloses.

UNIVERSITY OF ST. ANDREWS, Queen's College, Dundee
5 P.M. Dr. Ffrangcon Roberts: Acceptance of the Scientific Method of Medicine—its Origin, Evolution, and Consequences.

Friday, 27th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics*. Dr. J. H. Edwards, Dr. D. G. Harnden, Prof. L. S. Penrose, Dr. Paul Polani: Human Chromosomes in Relation to Disease in Childhood.
8.15 P.M. *Obstetrics and Gynæcology*. Mr. Frank Musgrove: Gynæcological and Obstetrical Impressions of a Visit to the United States. Miss M. Moore White: Uteroplasty in Infertility. Mr. D. J. MacRae, Mr. T. S. M. Barnett, Mr. Norman Smyth: Use of the Cardiophone in the Labour Ward.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. Ashton Miller: Pædiatric Urology.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. George Qvist: Surgery of the Lower Œsophagus.

INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W.C.1
4.30 P.M. Mr. Valentine Logue: Surgical Management of Cerebral Aneurysms.

ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1) *Medical Section*. Dr. N. T. J. Bailey, Mr. T. H. Hollingsworth, Dr. A. E. Maxwell: Related Variables in Medical Statistics.

Saturday, 28th

MEDICAL ASSOCIATION FOR THE PREVENTION OF WAR
2.30 P.M. (45, Russell Square, W.C.1.) Symposium on Present-day Significance of Medical Science in Relation to War Prevention.